

**The relationship between aortic aneurysm wall
distensibility and aneurysm growth and rupture**

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Declaration of Authorship

This thesis has been composed by the candidate and is entirely the work of the candidate unless otherwise stated. Ms AJ Lee of the Medical Statistics Unit, Public Health Sciences, University of Edinburgh carried out the Cox proportional hazard model analysis.

Katherine Ann Wilson

Acknowledgements

There are many people without whom a piece of work of this size could not be achieved. I will endeavour to name and thank all those who have supported me over the last four years but my sincerest thanks go to each and every one of my family, friends and colleagues who have given me all that I needed to complete this thesis.

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Dedication

This thesis is dedicated to my parents, Alice and Alan, my best friends.

Abstract

Introduction: Community mortality for ruptured abdominal aortic aneurysm (AAA) exceeds 80% and the operative mortality is 30-70%. Elective repair of AAA virtually eliminates the risk of rupture and is associated with an operative mortality of 5-10%. The decision to operate on an asymptomatic AAA, therefore, involves weighing the risk of rupture against that of surgical intervention. Rupture is related to maximum diameter, growth rate and possibly blood pressure, but no size of AAA is entirely free of rupture risk. A variable that provides a more precise quantification of rupture risk on an individual patient basis is required to improve the clinical and cost-effectiveness of surgery. AAA wall distensibility, which is measurable non-invasively, may be related to aortic wall structure and thus aneurysm growth and rupture.

Aims: The primary aim was to determine the relationships between AAA wall distensibility, diameter, expansion and risk of rupture. Secondary aims were to evaluate the variability of the technique and to assess the error caused by use of brachial, as opposed to central, blood pressure.

Methods: Distensibility [pressure-strain elastic modulus (E_p) and stiffness (β)] was measured using a real time B-mode ultrasound scanner with echo-tracking software (Diamove). Brachial pressure was measured using automated sphygmomanometry (Omron, Japan). Central aortic pressure was derived using pulse wave analysis (Sphygmocor). Follow-up was 6-monthly for a median (IQR) period of 19.7 (9.2-29.9) months. Outcome measures included ruptured AAA and surgical repair of intact AAA. Death certificate information was collected on those who died before the end of the study.

Results: 210 patients (163 males and 47 females) were recruited. Median (IQR) age was 72 (68-77) years, AAA diameter 48 (41-54) mm, BP 140/80 (128-160/ 72-90) mmHg, E_p 2.91 (1.99-4.37) 10^5Nm^{-2} , and β 19.4 (14.4-29.4). Intra- and inter-observer CV_{ME} for directly measured variables were low ($\leq 10\%$) while CV_{ME} for the derived variables were higher ($\leq 35\%$). The CV_{ME} is a parametric test; however, when these skewed data were logged to normality intra-observer CV_{ME} for β was $\leq 10\%$. Bland-Altman plots showed that E_p and β calculated using brachial, as opposed to derived central pressure, were systematically over-estimated by 11% ($p=0.001$) and 5% ($p=0.040$) respectively. At baseline, AAA in the rupture group tended towards being more distensible than the intact AAA but this did not attain statistical significance. At last follow-up, the rate and direction of change in distensibility were not related to diameter or expansion. Cox proportional hazard model showed that, after adjusting for age and sex, female gender, larger AAA diameter, higher diastolic pressure and a larger proportional increase in distensibility were related to a shorter time to rupture (all $p \leq 0.01$).

Conclusions: The relationships between AAA distensibility and rupture are complex and depend upon AAA diameter, gender and/or outcome group. Change in distensibility over time appears to be related to rupture risk. An increase in distensibility in conjunction with increasing diameter may indicate an increased risk of rupture.

Abbreviations

10^5Nm^{-2}	- 10^5 Newtons per metre ²
a.u.	- Arbitrary units
AAA	- Abdominal aortic aneurysm
ACE inhibitor	Angiotensin converting enzyme inhibitor
C	- Compliance
Ca channel blocker	- Calcium channel blocker
CABG	- Coronary artery bypass graft
CI	- Confidence interval
CV _{ME}	- Coefficient of variation of method error
β	- Stiffness
β -blocker	- Beta-blocker
D	- Distensibility
DBP	- Diastolic blood pressure
Dch	- Diameter change
Dmax	- Maximum diameter
Ep	- Pressure-strain elastic modulus
GTF	- Generalised transfer function
HT	- Hypertension
IQR	- Interquartile range
MAP	- Mean arterial pressure
mm	- Millimetres
mmHg	- Millimetres of mercury
MMP	- Matrix metalloproteinases
N	- Number analysed
p	- Significance level
PP	- Pulse pressure
PWV	- Pulse wave velocity
RR	- Relative risk
SBP	- Systolic blood pressure
SD	- Standard deviation
SE	- Standard error
SMC	- Smooth muscle cell
UKSAT	- United Kingdom Small Aneurysm Trial

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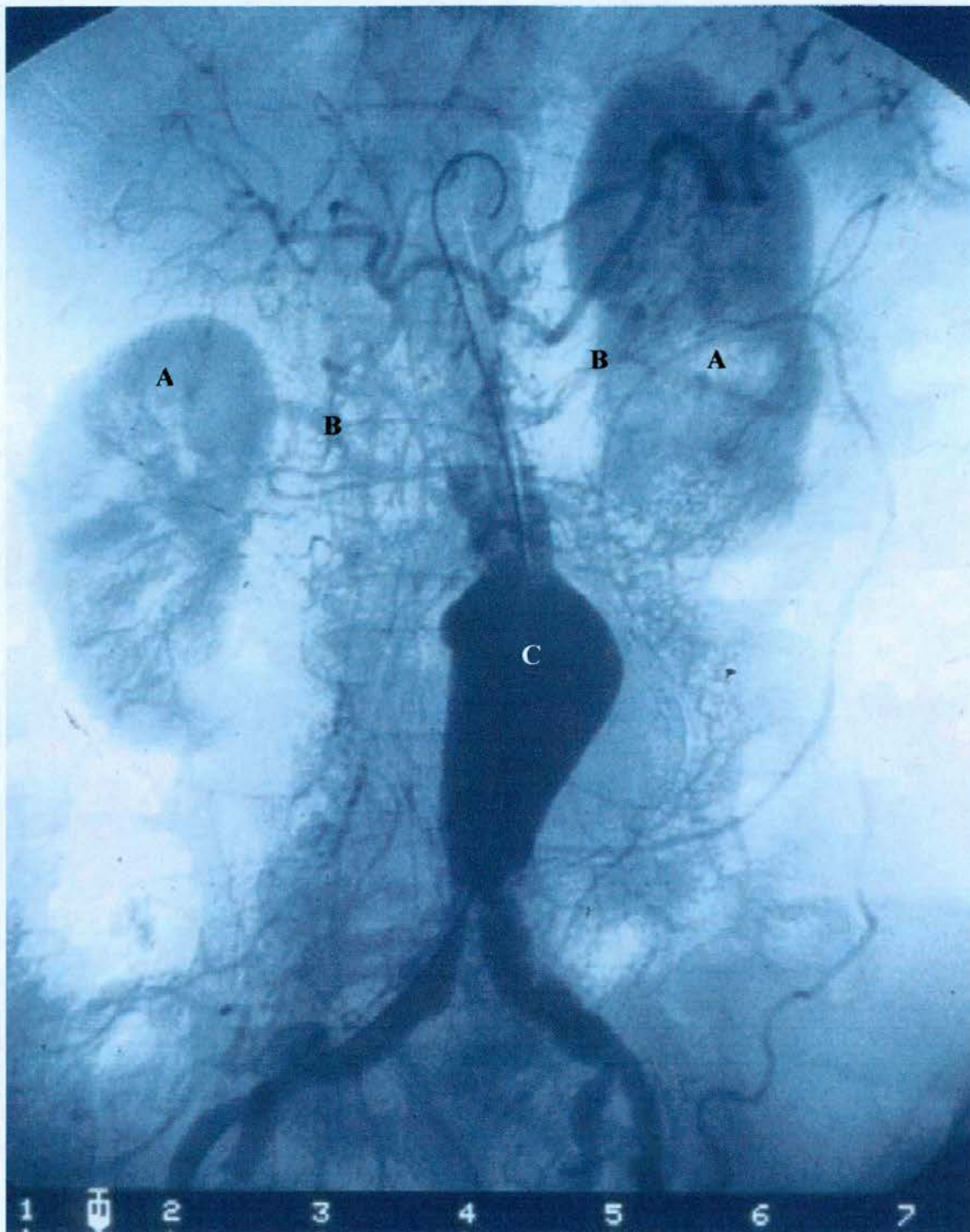
Chapter 1. Epidemiological Review

1.1 AAA

1.1.1 Definitions

An abdominal aortic aneurysm (AAA) may be defined as a localised dilatation of the abdominal aorta. AAA usually arise below the renal arteries (Figure 1.1), but around 20% also involve the suprarenal aorta. In men aged 65-75 years, the normal infrarenal aortic diameter is approximately 2cm (Hollier and Wisselink, 1996). The human aorta undergoes expansion throughout life, with a more rapid rate of expansion occurring over the age of 60 years (Lanne *et al*, 1994, Grimshaw *et al*, 1995). Sonesson *et al* (1993) found that the healthy male aorta expands by 30% between the ages of 25-70 years. Grimshaw *et al* (1995) observed that non-aneurysmal aortic dilatation occurs in 12.5%-25% of the population with increasing age. These observations imply that the threshold for distinguishing between normal and abnormal aortic diameter is age-dependent.

Figure 1.1. Percutaneous transluminal angiogram of an infrarenal AAA, showing the kidneys (A) and the renal arteries (B) above the AAA (C).



Courtesy of Dr P Allan, Department of Radiology, Royal Infirmary of Edinburgh.

Several definitions of AAA have been proposed:

- (1) Grimshaw *et al* (1995) suggested that in males at any age, the upper limit for 'normal' aortic diameter should result in 6% of the population having an 'aneurysm'. By this definition in males, the upper limit of normality in abdominal aortic diameter in 60 year olds should therefore be 24mm; in 70 year olds, 32mm; and in 75 year olds, 37mm.
- (2) The Society for Vascular Surgery and the International Society of Cardiovascular Surgery (SVS/ISCVS) defines an aneurysm as a 50% increase in the normal aortic diameter, adjusted for gender and radiological modality (Johnston *et al*, 1991) but not age. Moher *et al* (1992) calculated mean aortic diameter in unaffected males to be 2.0cm. An AAA could therefore be said to be present when the maximum infrarenal diameter reaches 3.0cm. This definition, however, results in a higher prevalence of AAA because it will include age-related, non-aneurysmal dilatation.
- (3) Sterpetti *et al* (1987) suggested that an infrarenal AAA should be defined by the presence of an infra- to suprarenal diameter ratio of ≥ 1.5 . However B-mode ultrasonography cannot reliably image the suprarenal aorta making calculation of this ratio difficult for screening purposes.
- (4) Collin (1990) deemed an infrarenal AAA to be present when the maximal diameter was ≥ 4.0 cm, or when it exceeded the maximum diameter of the aorta between the origin of the superior mesenteric and left renal arteries by 0.5cm. This definition has the advantage of preventing unnecessary follow-up of age-related dilatation, although fast growing AAA may be missed if follow-up is deemed unnecessary in small AAA. The use of a larger diameter in this definition produced the lowest frequency and prevalence rates in Moher *et al*'s (1992) study.

None of these definitions is perfect. For the purposes of this thesis, therefore, an AAA has been defined as a maximal infrarenal antero-posterior diameter of $\geq 3.0\text{cm}$ (Moher *et al* 1992, Bengtsson *et al* 1996).

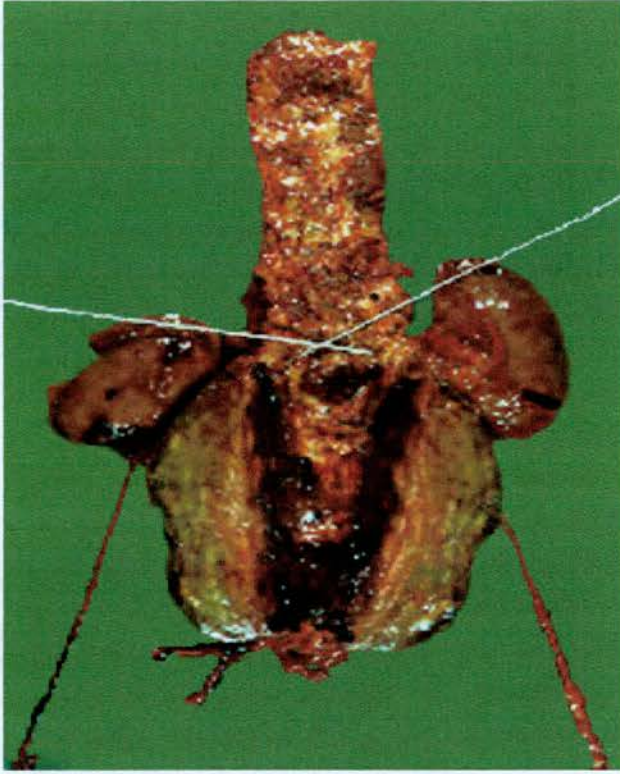
1.1.2 Classification

Aneurysms are usually classified according to their pathology, shape, site and aetiology:

True aneurysm: - The aneurysm wall comprises all three layers of the normal arterial wall. The vast majority of AAA are of this type (Figure 1.2).

False aneurysm: - The aneurysm wall comprises only compressed peri-adventitial tissue. It usually occurs following trauma or at the site of graft-arterial anastomoses.

Figure 1.2. A true AAA involving the full thickness of the wall

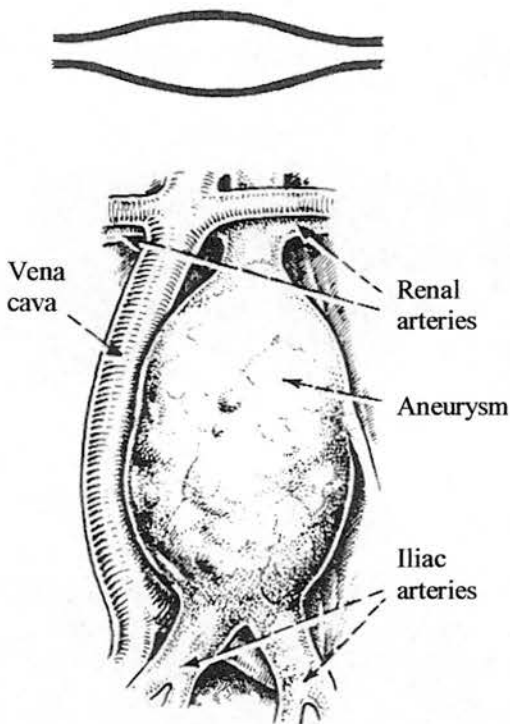


Courtesy of Dr K McLaren, Department of Pathology, University of Edinburgh.

Fusiform aneurysm: - The aneurysm is spindle shaped and most AAA are of this type (Figure 1.3).

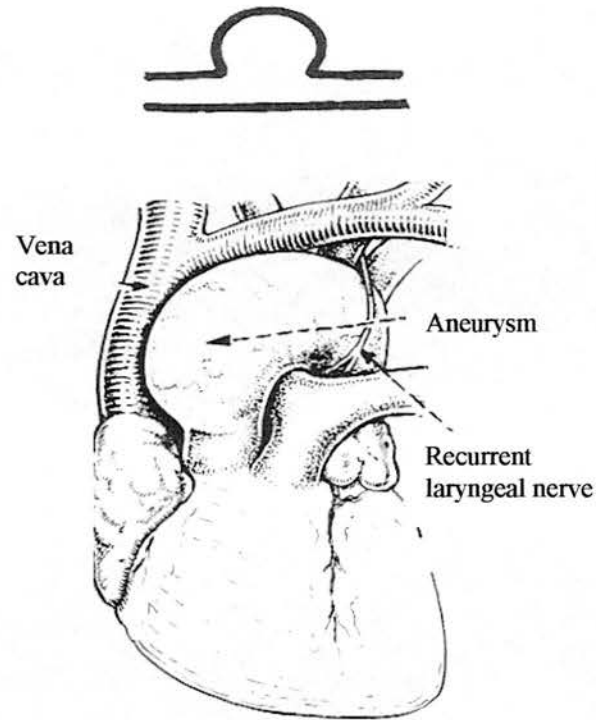
Saccular aneurysm: - The aneurysm is an out-pouching of the arterial wall localised to one side of the artery (Figure 1.4).

Figure 1.3. Fusiform aneurysm



McFarlane *et al* (2000)

Figure 1.4. Saccular aneurysm



Atherosclerotic aneurysm: - Historically those AAA thought not to be due to a specific and recognised cause such as connective tissue disorder, trauma or infection have been termed atherosclerotic. However, it has become increasingly apparent that the majority of AAA are not due to atherosclerosis but to a distinct disease process. For example, in AAA formation most of the pathological changes occur in the media whereas in atherosclerosis the pathological damage is predominantly subintimal (Hollier and Wisselink, 1996, Stonebridge and Ruckley, 1996). The SVS/ISCVS have therefore recommended the term ‘non-specific’, rather than ‘atherosclerotic’, be used (Johnston *et al* 1991).

Inflammatory aneurysm: - Inflammatory AAA account for around 5-10% of all AAA and are characterised by marked retroperitoneal fibrosis, lymphocytic and plasma cell infiltration. It is said that these AAA are less prone to rupture but there is no convincing evidence for this. However, surgical repair is undoubtedly made more hazardous because of the dense fibrosis between the AAA wall and adjacent structures (Stonebridge and Ruckley, 1996).

1.1.3 Site of aneurysmal development

Aortic aneurysms most commonly affect the infrarenal aorta but can also affect the suprarenal and thoracic segments. The distal aorta appears to be at particular risk, possibly because of its reduced number of elastic lamellae (when compared with the thoracic aorta) and the lack of vasa vasora. Reflected waves from the aortic bifurcation may also present a hazard by increasing systolic and pulse pressure. However many patients with AAA also have peripheral aneurysms suggesting that it may be a systemic disease (Hollier and Wisselink 1996).

1.1.4 Clinical presentation

Most patients (75%) with AAA are asymptomatic and their aneurysms tend to be diagnosed incidentally during radiological or physical examination carried out for another reason (Hollier and Wisselink 1996) (Figure 1.5). The majority probably die with an intact AAA rather than of a ruptured AAA.

Symptoms are caused by pressure on adjacent structures, embolisation, dissection, thrombosis or rupture and include:

- (1) Pain – This may be due to pressure on adjacent structures or nerves and typically radiates to the back or loins;
- (2) Embolisation – This may lead to ‘blue toe’ syndrome if emboli are small, or acute lower limb ischaemia if large;
- (3) Rupture – Sudden onset of mid-abdominal and/or flank pain with shock and a pulsatile abdominal mass typically suggests AAA rupture. The pain can be severe, constant and unaffected by position or it can be more subtle, lasting for several hours or days. The latter type of pain may be from small tears in the AAA wall that are temporarily sealed by thrombus but this will eventually lead to rupture (Hollier and Wisselink 1996).

Figure 1.5. Ultrasound of longitudinal view of anteroposterior section of AAA.



Courtesy of Dr P Allan, Department of Radiology, Royal Infirmary of Edinburgh.

1.2 Aetiology of AAA

1.2.1 Epidemiological difficulties

Epidemiological data on AAA are difficult to gather because;

- a) The disease is mostly asymptomatic.
- b) Many patients present for the first time with rupture.
- c) Many AAA-related deaths are probably misdiagnosed, for example as sudden cardiac death, because a post mortem is not performed.
- d) The lack of a universally accepted definition of AAA causes difficulty in determining the prevalence of the disease (section 1.1.1).

1.2.2 Trends in AAA

The prevalence of AAA varies enormously depending on the definition used and the methodology employed (Moher *et al* 1992) (Table 1.1). Post mortem studies provide frequency rates but unless necropsy rates are 100% they cannot estimate prevalence in the population. Post mortem studies are usually retrospective and the diagnostic criteria are rarely clarified prior to diagnosis, making comparison with other studies difficult (Bengtsson *et al* 1996).

There is evidence of a recent rise in the prevalence of AAA in Western countries. For example, in Sweden, Bengtsson *et al* (1996) found that age-standardised AAA frequency from 1958 to 1986 had increased annually at a rate of 4.7% in men and 3.0% in women. In the Netherlands, Reitsma *et al* (1996) found that between 1972 and 1992 AAA-related mortality in males increased from 3.1 to 8.1 per 100,000, and in females from 1.4 to 2.2 per 100,000. In the same study, total hospital admissions for non-ruptured AAA increased 13-fold in males and 6-fold in females. In the UK, AAA prevalence is estimated to range from 1.3 to 8.4 % (Lucarroti *et al* 1993, Scott *et al* 1995, Smith *et al* 1993) (Table 1.1).

The reported incidence rate of AAA rupture ranges from 2.9 (Armour 1977) to 14.1 (Thomas and Stewart 1988) per 100,000 per year. Surgical workload has undoubtedly increased in the last two decades (Crawford 1990, Castleden and Mercer 1980, Melton *et al* 1984). In the Edinburgh Regional Vascular Unit, 85.4 % of patients presenting with rupture were operated between 1989 and 1994 compared with 77% presenting between 1983 and 1988 (Bradbury *et al* 1997) (Figure 1.6).

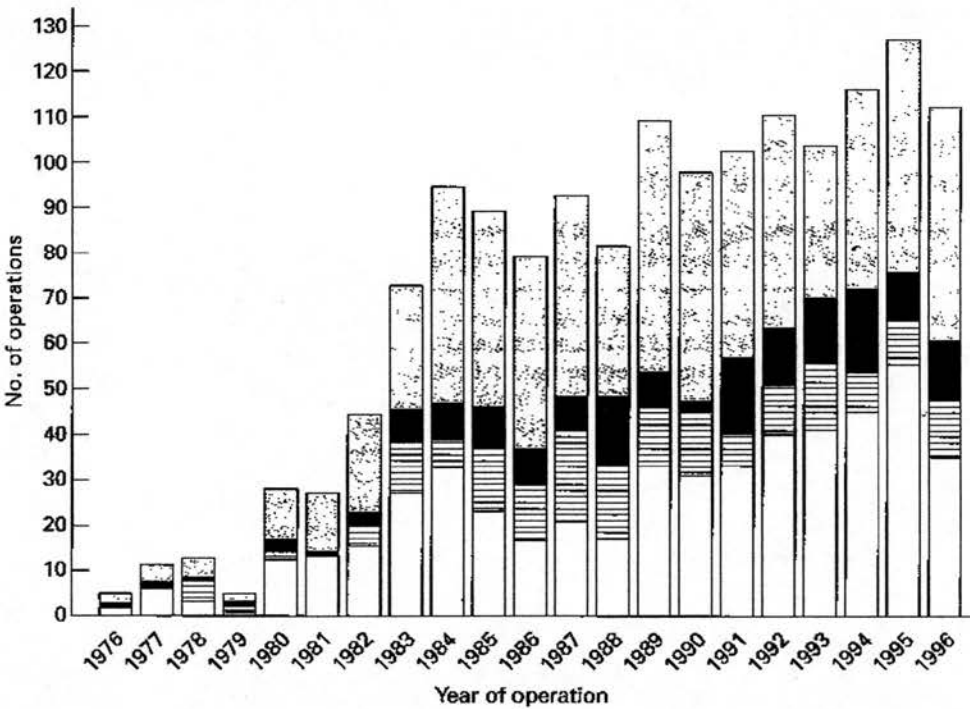
Table 1.1. Prevalence and frequency of AAA from a selection of studies.

	Prevalence (%)	Definition and inclusion criteria
Lederle <i>et al</i> 1997	4.6	≥3cm
	1.4	≥4cm
	0.5	≥5cm
	0.2	≥6cm
Moher <i>et al</i> 1992	12.1	≥1.5 x infrarenal aortic diameter*
	6.1	≥1.5 x suprarenal aortic diameter**
	3.5	≥4cm or 1.5 x suprarenal aortic diameter [⊖]
Morris <i>et al</i> 1994	2.3	age 50-64 yrs
	8.8	age 65-79 yrs } all ≥2.9cm
	11.9	age >80 yrs
Scott <i>et al</i> 1995	3.0	males, 65-80 yrs, >2.9cm
	1.3	females, 65-80 yrs, >2.9cm
Smith <i>et al</i> 1993	8.4	males, 65-75 yrs, >2.9cm
	3.0	males, 65-75 yrs, >4cm
Lucarotti <i>et al</i> 1993	8.4	males, 65 yrs, >2.5cm
	1.3	males, 65 yrs, >4cm
Bengtsson <i>et al</i> 1996	<u>Frequency (%)</u>	
	3.2	All, ≥3cm
	5.2	males, 75-79 yrs, ≥3cm
	1.7	females, 75-79 yrs, ≥3cm

* Johnston *et al* (1991); ** Sterpetti *et al* (1987); [⊖] Collin (1990)

Figure 1.6. Number of, and indication for, AAA repair between 1976 and 1996 in the Edinburgh Regional Vascular Centre.

Asymptomatic;
 Symptomatic elective;
 Symptomatic emergency;
 Rupture



1.2.3 Prognosis of AAA

In the UK, it is estimated that 1.7% of men aged 65-74 years die from AAA (Collin 1990). Approximately 900 people die annually from ruptured AAA in Scotland (Naylor *et al* 1988). Many of these patients do not reach hospital alive (Drott *et al* 1992, Choksy *et al* 1999) and of those who do, approximately 40-55% will die (Samy *et al* 1994, Bradbury *et al* 1997). Despite considerable surgical and anaesthetic specialisation, the mortality associated with (attempted) repair of ruptured AAA shows

no sign of decreasing, and may in fact be rising. This is likely to be due to increased numbers of elderly and infirm patients being operated (Bengtsson *et al* 1996).

Natural history:- In 1950, before surgical repair was available, Estes *et al* (1950) found the 1-year survival of AAA subjects to be 60%, and the 5-year survival to be only 19%. Furthermore, 63% of these patients died from AAA rupture. Although this study is now 50 years old and no recent, non-interventional, natural history data are available, other data support this poor prognosis (Klippel and Butcher 1966, Darling *et al* 1977). On the basis of these data it has generally been taught that the majority of patients with AAA should undergo surgical repair. More recently however, the UK Small Aneurysm Trial (UKSAT) found that over a three year period, the annual rupture rate of a cohort of subjects with AAA 3-6cm in diameter was 2.2% when undergoing ultrasound surveillance. This included patients deemed unfit for surgery. Annual rupture rate in the 4-5.5cm group who were randomised to surgery or observation was found to be only 1% with ultrasound surveillance (Brown and Powell 1999).

Rupture risk:- Age- and sex-adjusted maximum diameter is currently believed to be the most important and easily measurable variable affecting rupture risk (Millis *et al* 1992). Around 20% of 5-7cm AAA ruptured within a year. The annual risk of rupture progressively increases with aneurysm size to around 60% if the diameter is greater than 10cm (Darling 1970, Millis *et al* 1992) (Table 1.2). The UKSAT reported crude rupture rates (per 100 person-years) to be 0.3 in AAA of ≤ 3.9 cm, 1.5 in AAA of 4.0-4.9cm and 6.5 in AAA of 5.0-5.9cm (Brown and Powell 1999). These diameters were those known or estimated at time of rupture.

Although without surgery ruptured AAA is universally fatal, the results of (attempted) repair remain disappointingly high (Table 1.3) and show no sign of improving (Bradbury *et al* 1998). Mortality following emergency repair of ruptured AAA in non-specialist centres can be as high as 50% (Katz *et al* 1994, Johnston 1994). By contrast, the mortality associated with elective repair has fallen to about 6%. The challenge, therefore, is to be able to identify those individual patients at highest risk of rupture and lowest risk of elective repair, and operate upon them at the earliest opportunity.

Table 1.2. Estimated risk of survival, rupture and surgical repair.

1 year survival (all diameters) with no follow-up or intervention* Estes (1950)	60%
5 year survival (all diameters) with no follow-up or intervention* Estes (1950)	19%
5 year risk of rupture (all sizes) 5 year risk of elective repair (all sizes) Galland <i>et al</i> (1998)	15% 26%
AAA < 4cm 5 year risk of rupture 5 year risk of elective repair Galland <i>et al</i> (1998)	4% 13%
AAA 4-5.5cm 5 year risk of rupture 5 year risk of elective repair Galland <i>et al</i> (1998)	21% 42%

*Data from 1950 when ultrasonic follow-up and surgical repair were not available

Table 1.3. 30-day mortality following surgical repair of AAA.

	30-day mortality* (%)
Elective asymptomatic repair	6.1
Elective symptomatic repair	5.8
Emergency symptomatic non-ruptured repair	14.1
Emergency rupture repair	37.0

*Also same-admission mortality as some die after 30 days but during initial admission (Bradbury *et al* 1998).

Prognosis following non-ruptured repair:- Surgical mortality in individual case series of asymptomatic elective AAA repair has been reported to be as low as 1-5% (Hollier and Wisselink 1996). The UKSAT showed the 30-day operative mortality in 4-5.5cm AAA to be 5.8% (The UK Small AAA Trial Participants 1998). In Edinburgh, over a 21-year period, the operative mortality was similar at 6.1% for asymptomatic elective repair and 5.8% for symptomatic elective repair (Bradbury *et al* 1998). In contrast, patients operated as an emergency have a 14-37% mortality rate (Bradbury *et al* 1998). Patients who survive elective AAA repair return to a (near) normal life expectancy. This is partly because high-risk patients with major cardiac disease are, in general, not offered (or do not survive) surgery. After repair of ruptured AAA, the long-term survival also approaches normality, again because the very high-risk patients are not operated or die in the early post-operative period (van Ramshorst *et al* 1990).

1.2.4 Risk factors for AAA

AAA and atherosclerosis frequently co-exist in the same patient and appear to share common risk factors:

Smoking:- Tobacco is the major 'environmental' agent implicated in AAA formation. The association between smoking and aneurysmal disease appears to be stronger than that between smoking and coronary heart disease (Hollier and Wisselink 1996).

Wilmink *et al* (1999a) suggested that smoking results in AAA elastolysis.

MacSweeney *et al* (1994a and b) suggested that smokers have higher AAA growth rates than ex-smokers and that smoking increases the likelihood of death from AAA. It is also apparent that heavy smokers who inhale deeply have the highest risk of AAA among current and ex-smokers (Franks *et al* 1996, Brown and Powell 1999).

Hyperlipidaemia:- It has been suggested that hyperlipidaemia, leading to atheromatous plaque deposition, may be associated with AAA progression, dissection and rupture (Hollier and Wisselink, 1996). However, other population-based studies have not confirmed this (Wilmink and Quick 1998). Furthermore, Limet *et al* (1998) reported that monkeys fed an atherogenic diet failed to develop AAA.

Hypertension: - Hypertension has also been shown to be related to increased AAA expansion and rupture (Hollier and Wisselink 1996, Stonebridge and Ruckley 1996). Over 40% of AAA patients are hypertensive (Hollier and Wisselink 1996), as are 70% of dissecting AAA patients (Millis *et al* 1992). Cronenwett (1996) suggested that hypertension is a major risk factor for AAA rupture. Diastolic hypertension may be associated with a 3 to 4-fold increase in the risk of developing an AAA (Franks *et al* 1996). The role of hypertension in aneurysm development, progression and rupture is complex and not clearly understood. However, since AAA growth depends on the intrinsic strength of the aortic wall and the pressure exerted upon it by the flowing blood, hypertension is an obvious risk factor for AAA development and progression.

Gender: - AAA prevalence is higher in males. Despite this, rupture risk appears to be as much as three times higher in females than in males (Brown and Powell 1999).

Age: - Advancing age itself is an important risk factor, the incidence being higher in those over 60 years (Hollier and Wisselink 1996). However, 25% of the population over 60 years of age have age-related aortic expansion as opposed to true AAA

development (Grimshaw and Thompson 1997). The peak prevalence of rupture is between 70 and 75 years of age (Grimshaw and Thompson 1997).

Genes: - There is a familial tendency to AAA, with around 30% of brothers and 5% of sisters being affected (Bengtsson *et al* 1989). Limet *et al* (1998) found that male patients with familial AAA were significantly younger at diagnosis and at rupture, and had a significantly higher rupture rate (32%) than those with sporadic AAA. Studies of genetic variations in AAA disease have so far produced contradictory evidence of possible pathways (Cohen *et al* 1990, Majumder *et al* 1991, Powell *et al* 1993, Ramsbottom *et al* 1994, Elzouki and Eriksson 1994, Verloes *et al* 1995). Inheritance of AAA disease may be multifactorial; the result of a complex interaction between environmental factors and genetic susceptibility. Despite familial clustering and the investigation of several genes, the genetic basis of AAA formation remains obscure (Wills *et al* 1996a).

1.2.5 The role of atherosclerosis

Although atherosclerosis and aneurysm commonly co-exist, the former is thought to be an associated factor rather than the cause of aneurysm formation. The two diseases may have the above risk factors in common, however, the following arguments suggest that AAA and atherosclerotic occlusive disease are distinct and separate conditions (Limet *et al* 1998).

- There are distinct pathological differences between the two diseases. For example, AAA morphology shows marked attenuation of the media compared with the well-developed media in aorto-occlusive disease.

- Experimental atherogenic models have not consistently produced AAA
- Evidence suggests a genetic predisposition to AAA
- Specific alterations of collagen and elastin occur in AAA but not in atherosclerosis
- Inflammatory infiltrate (T and B-lymphocytes, mast cells and macrophages) is present in AAA wall, predominantly in the media and at the medial-adventitial Junction (Satta *et al* 1998)
- Enzymatic activation leads to proteolysis by matrix metalloproteinases (MMP's) in AAA

1.3 Surgical treatment

Open AAA repair is one of the commonest procedures carried out by vascular surgeons. There are several operative approaches, but all involve clamping the neck of the aneurysm and the iliac arteries. The sac is then opened and the laminated thrombus removed. Bleeding lumbar arteries are suture ligated and a prosthetic graft inserted. The sac is then closed over the graft.

1.3.1 Risk-benefits of surgical repair

The decision to operate on an AAA involves weighing the risk of rupture against the risk of surgery for each individual patient. Important factors include:

- i) AAA diameter
- ii) The presence of symptoms
- iii) The presence of concomitant disease, notably cardiac, respiratory and renal disorders.

The UKSAT (The UKSAT Participants 1998) has recommended that ultrasonographic surveillance of AAA ≤ 5.5 cm in diameter is safe and that early surgical repair of these AAA does not provide a long-term improvement in survival. Mortality following repair of AAA with diameters of 4-5.5cm was not improved at 2, 4 and 6 years when compared with the surveillance group (The UKSAT Participants 1998).

1.4 Pathophysiology of AAA

1.4.1 Normal aortic wall

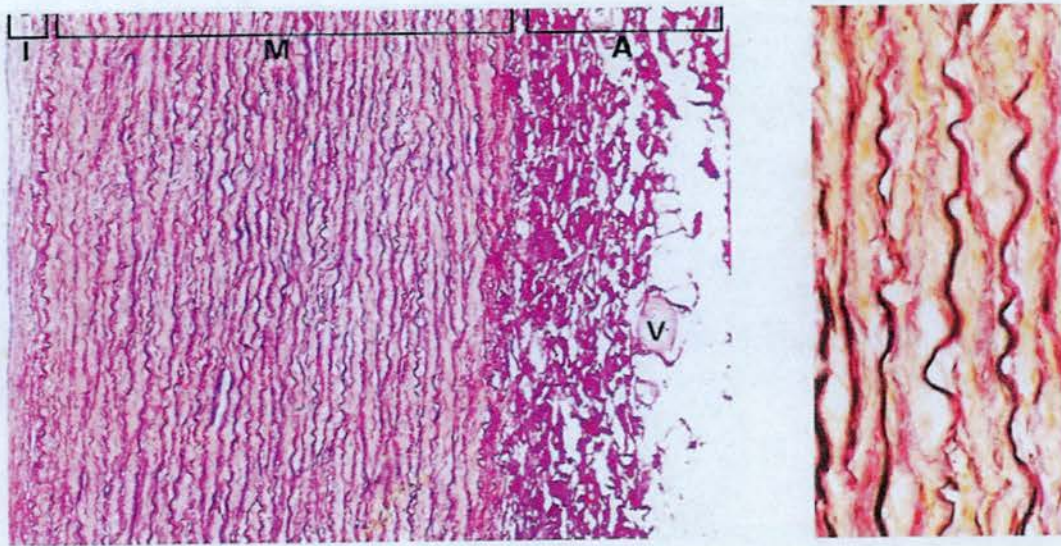
The normal aorta is an elastic artery comprising three layers (Figure 1.7):

Intima:- The intima is the innermost layer comprising a single layer of endothelial cells supported by elastin-rich collagenous tissue (Burkitt *et al* 1993). The internal elastic lamina separates the intima from the media. The subendothelium comprises fibroblasts and myointimal cells. With increasing age, the myointimal cells accumulate lipids and the intima progressively thickens.

Media:- The media comprises concentric layers of fenestrated sheets of elastic lamellae and circumferentially oriented collagen fibres. Each layer of collagen runs alongside a network of fine elastin fibres with a layer of smooth muscle cells (SMC) compacted between adjacent elastic lamellae (Wills *et al* 1996a). The SMC in the media are responsible for the mechanical properties of the aorta and for the production of the extracellular matrix (He and Roach 1994), while the close association of elastin, collagen and SMC provides the viscoelastic properties. The extracellular matrix contains microfibrillar proteins that are closely associated with the medial elastic lamellae.

Adventitia:– The adventitia comprises collagen, scattered elastin fibres, fibroblasts that synthesise extracellular matrix proteins, and inflammatory cells (Wills *et al* 1996a). There is a network of vasa vasora (relatively scant in the infra-renal aorta in comparison with that of the thoracic aorta) which penetrate the outer half of the media. [Details of elastin and collagen within the AAA wall are described in Sections 1.4.3 and 1.4.4].

Figure 1.7. Micrograph of the normal aorta on the left including the intima (I), the media (M) and the adventitia (A) containing vasa vasorum (V). The image on the right shows the concentric fenestrated sheets of elastin (black) separated by collagenous tissue (red) and smooth muscle cells (yellow) in the media (Young and Heath 2000).



Elastic Van Gieson x33

Elastic Van Gieson x320

1.4.2 The aneurysmal aortic wall

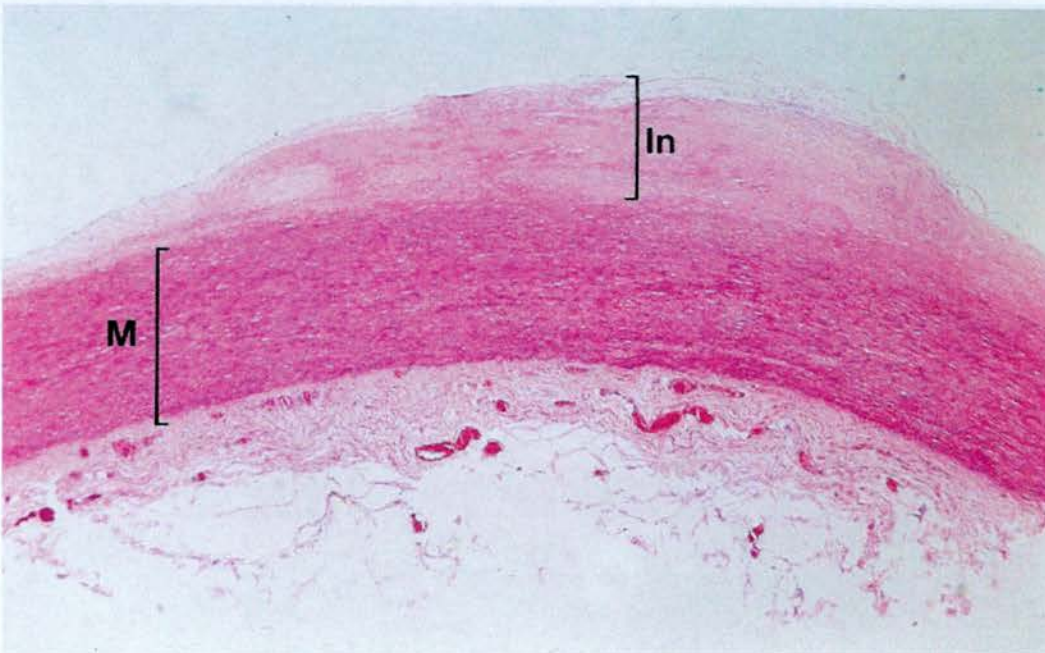
Intima:– The intima becomes thickened because of aggregated myointimal cells that have taken up lipid (Figure 1.8). Laminated thrombus is deposited on the intimal surface. There is an increased volume of disorganised collagen and elastin and the

internal elastic lamina is variably destroyed making it difficult to distinguish the intima from the media (Limet *et al* 1998).

Media:— The media becomes attenuated due to the loss of supporting elastic tissue, atrophy of smooth muscle cells and progressive medial fibrosis. The medial lamellar units become disorganised and damaged and the elastin fibres become fragmented (Wills *et al* 1996b, Ghorpade and Baxter 1996). Eventually the medial fibrous tissue stretches because of the loss of elastic recoil and the artery dilates (Figures 1.10 and 1.11).

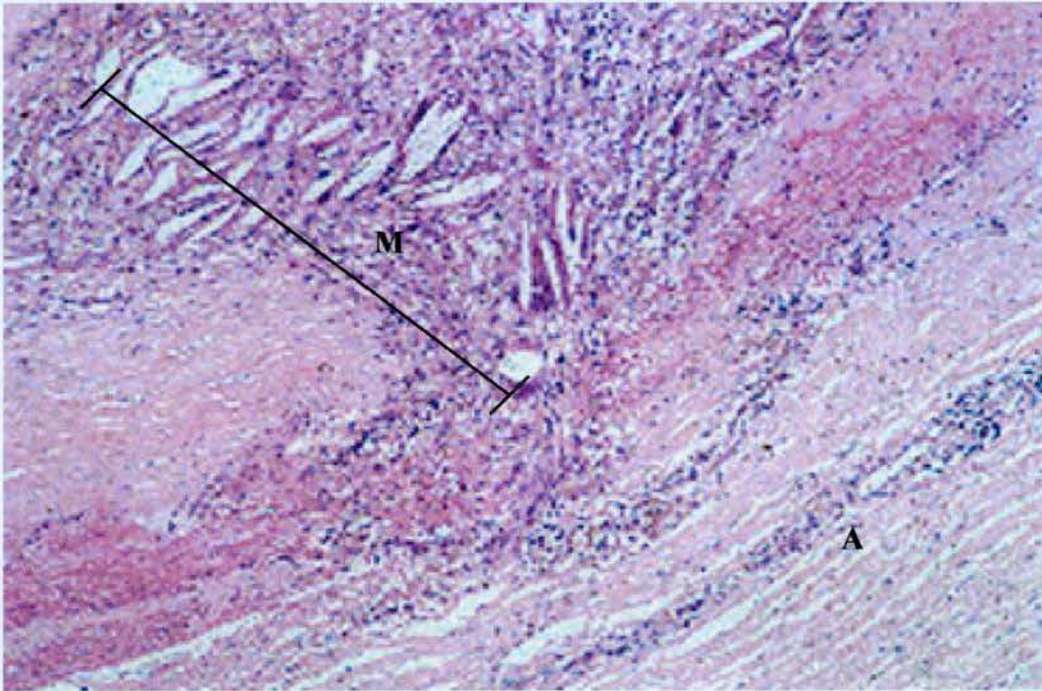
Adventitia:— In order to maintain its original thickness, the circumferential area of the adventitia increases. This involves the synthesis and accumulation of matrix proteins such as fibrillin (Halloran and Baxter 1995, Wills *et al* 1996a).

Figure 1.8. Early aneurysmal changes in the aorta; (In) represents thickening of the intima, (M) shows the media which has not yet undergone degeneration or attenuation (Burkitt *et al* 1996)



Haematoxylin and eosin, low power.

Figure 1.9. Photomicrograph of the AAA wall; (M) shows medial infiltration by cholesterol deposits and disruption of the lamellar units, and (A) the adventitial thickening (Courtesy of Dr K McLaren, Dept. Pathology, University of Edinburgh).



Haematoxylin and eosin, high power.

1.4.3 The role of collagen and elastin in the non-aneurysmal aorta

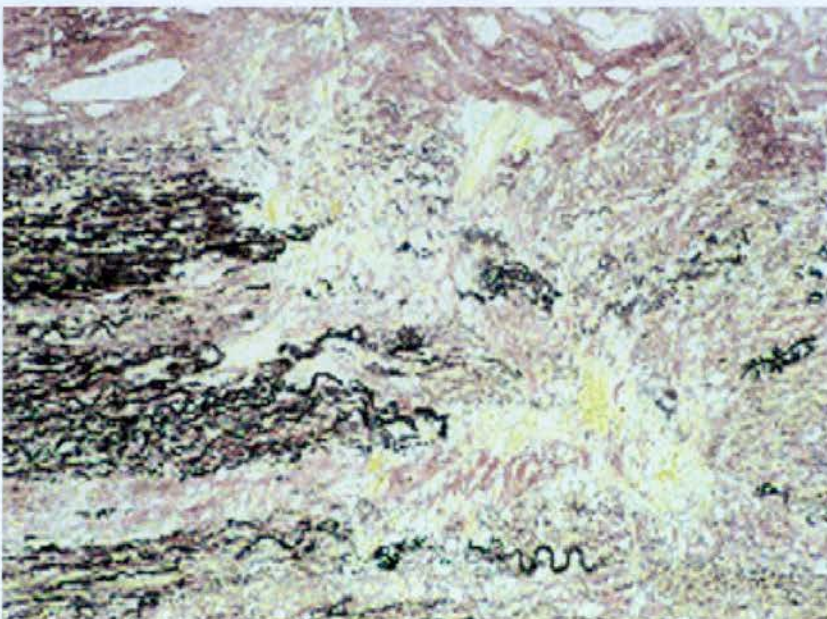
Collagen and elastin have quite distinct mechanical roles in the aorta. Elastin expands by 50-70% of its original length and bears most of the stress at low pressures. It also allows stress to be distributed uniformly throughout the wall and maintains the equilibrium between mural haemodynamic stress and the resultant deformation.

Collagen expands by only 4% of its original length. However, it is coiled in such a way that it allows elastin to stretch in response to the cardiac cycle and provides tensile strength at high pressures, thus preventing over-distension (MacSweeney *et al* 1994a).

1.4.4 Collagen and elastin in AAA

Aneurysmal formation and expansion occur in response to the degradation and remodelling of elastin and collagen fibres (Figure 1.10). These changes are the result of increased proteolytic activity consequent upon macrophage and lymphocyte infiltration of the AAA wall (Anidjar *et al* 1994, Halloran and Baxter 1995, Lopez-Candales *et al* 1997). There is an increase in total protein, microfibrillar protein (possibly fibrillin) and collagen content but a reduction in elastin concentration and medial SMC (Sumner *et al* 1970, He and Roach 1994, Gandhi *et al* 1994, Wills *et al* 1996a). The result is a relative imbalance in the structural proteins.

Figure 1.10. Photomicrograph showing breakdown of elastin; the concentric layers of elastin are fragmented (black), (Courtesy of Dr K McLaren, Dept. Pathology, University of Edinburgh).



Elastin Van Gieson, High Power

Elastin degeneration:— Elastin degeneration appears to occur early in AAA development (Dobrin *et al* 1984, White and Mazzacco 1996, Limet *et al* 1998). Compared with the non-aneurysmal aorta, the volume fractions of both elastin and SMC in AAA are decreased considerably (90%) (He and Roach 1994, Lopez-Candales *et al* 1997). Total elastin concentration of the aneurysmal infrarenal aorta has been reported to be only 5-8% compared with the 15-35% found in age matched, non-aneurysmal controls (Powell and Greenhalgh 1989). Although the total elastin content of the aorta has been shown to increase, elastin concentration decreases because of the increased total protein content of the thickened aortic wall (Baxter *et al* 1994, Minion *et al* 1994, Sumner *et al* 1970).

There is disagreement among authors as to the cause of the reduced elastin concentration. Elastin gene expression is unaltered in AAA, whereas mRNA levels for the collagen precursor, α 1-procollagen, are increased. This suggests that discordant gene expression is responsible for the change in elastin and collagen concentration (Mesh *et al* 1992). Other authors suggest that selective degradation of elastin in the aneurysmal media would result in an apparent increase in collagen concentration (Menashi *et al* 1987). Whatever the mechanism, it would appear that elastin may not actually be lost but simply altered and redistributed over a larger area (Halloran and Baxter, 1995).

The rate of elastin degradation depends upon the balance between elastases and their inhibitors (anti-proteases). Cohen *et al* (1987) found aortic wall elastase to be significantly higher in patients with ruptured AAA than in those undergoing elective repair and higher still than those with aortic occlusive disease. Neutrophil elastase is

modified by the major protease inhibitor α_1 -antitrypsin, forming elastase α_1 -antitrypsin complexes. Increased serum-elastin-peptide (SEP) concentration indicates elastolysis (Sata *et al* 1998, Rao *et al* 1996) and has been suggested as a method of monitoring the degradation of elastin (Lindholt *et al* 1997).

Collagen synthesis and lysis:– Collagen types I and III predominate within the aortic wall. Type III providing most of the walls tensile strength. It has been hypothesised that an increase in proteolytic (MMP-9) activity in AAA leads to collagen destruction and, consequently, allows aneurysm growth and rupture (McMillan *et al* 1997). However, there is also an increase in collagen metabolism that involves a complex remodelling process. During this process, neosynthesis of collagen fibres and thickening of the intimal and advential layers compensate for the haemodynamic disequilibrium caused by elastolysis and collagenolysis, avoiding rupture at this stage.

The aminoterminal propeptide of type III procollagen (PIIINP) is released into the extracellular fluid (Prockop *et al* 1979) and is measurable in the serum. Satta *et al* (1995) demonstrated an apparent increase in PIIINP in patients with AAA compared with controls and suggested that this may be due to a combination of both enhanced synthesis and enhanced degradation of collagen. Indeed, volume fractions of collagen and ground substance are increased by approximately 80% in AAA (He and Roach 1994). Treska and Topolcan (2000) found AAA wall PIIINP to be significantly higher in larger AAA. However, this newly formed collagen may be weaker and more prone to proteolytic degradation (Sakalihasan *et al* 1993). Subsequently, inflammatory infiltrates, lymphocytes and macrophages cause dissociation of the collagen fibres. The loss of

tensile strength and thinning of the aortic wall leads to expansion of the aorta until eventually rupture may occur.

1.4.5 Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a family of zinc-based enzymes that selectively degrade the extracellular matrix of the aortic wall (Table 1.4). Endogenous tissue inhibitors of metalloproteinases (TIMPs) inhibit the activity of these MMPs. It is now accepted that increased elastase, collagenase and gelatinase activity plays a central role in aortic wall degeneration and AAA formation (Wills *et al* 1996a).

The MMPs present in elevated levels in AAAs have a synergistic effect stimulating the initiation and maintenance of extracellular matrix degradation of the media. MMP-9 can degrade elastin and denatured collagen, and facilitates the action of interstitial collagenase on collagen types I and III. Active forms of MMP-3 and plasmin lead to activation of MMPs -1 and -9, which in turn degrade elastin, fibrillar collagens and other matrix components (Vine and Powell 1991, Newman *et al* 1994a, Newman *et al* 1994b). The actions of the MMPs involved in AAA formation are tabulated in Table 1.4.

Table 1.4: Matrix metalloproteinases and their endogenous enzyme inhibitors (Thompson and Parks 1996).

Enzyme (MMP)	Producing cell type	Matrix substrates
Interstitial collagenase (MMP-1)	Smooth muscle cells macrophages, fibroblasts mesenchymal cells	Fibrillar collagen types I, II, III
72-kDa Gelatinase (MMP-2)	Smooth muscle cells macrophages	Collagen types IV, V, VII, X, elastin
Stromelysin-1 (MMP-3)	Smooth muscle cells	Proteoglycans, collagen types IV, V, IX, X
92-kDa Gelatinase (MMP-9)	Macrophages	Collagen types IV, V, VII, X, elastin

1.4.6 Inflammation

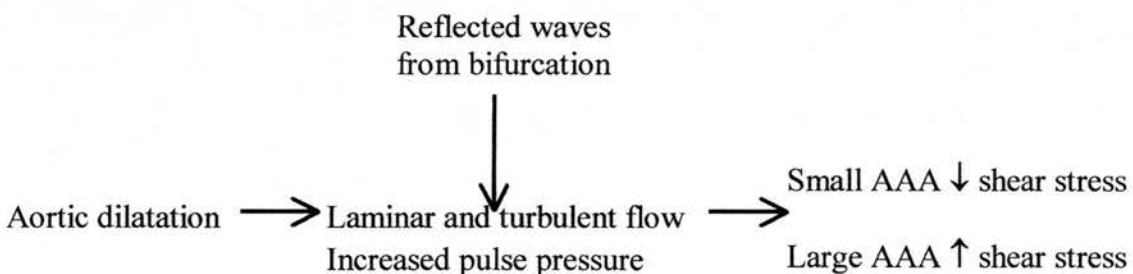
Inflammatory infiltrate is present in varying degrees in most AAA (Newman *et al* 1994c, Freestone *et al* 1995). T- and B- lymphocytes and macrophages are the predominant inflammatory cells found in the walls of AAA (Freestone *et al* 1995, Satta *et al* 1998) and are concentrated around the vasa vasorum at the medial – adventitial junction. These cells produce MMP–1, –2, and –9, which act specifically on elastin and collagen (Wills *et al* 1996b). Satta *et al* (1998) found that loss of elastin was related to the quantity of inflammatory cells present in the wall.

The lymphocytes and macrophages also activate resident mesenchymal cells by cytokinetic control mechanisms (Wills *et al* 1996a). Many cytokines [e.g. tumour necrosis factor- α (TNF- α), interleukin (IL)-1 β , –6 and –8, monocyte chemoattractant protein-1 (MCP-1)] with pleiotropic and often incompletely defined affects are involved. However, the key processes appear to be upregulation of adhesion molecules, activation of proteases and the eventual destruction of collagen and elastin.

1.4.7 Haemodynamic influences

Aneurysms occur most frequently in the abdominal aorta where there are unique haemodynamic conditions (Figure 1.11). As the aorta descends from the thorax to the abdomen, it tapers and becomes less distensible. This results in increased pulse pressure that is highest in the infrarenal aorta. Pressure waves are reflected from the aortic bifurcation further increasing pressure in the infrarenal aorta. The reflected waves also result in lower, and even negative, shear stress at the aortic wall. Low shear stress promotes atherosclerotic plaque formation because of stagnant blood flow (Sumner 1995). Model studies of AAA have suggested that laminar blood flow may predominate in smaller AAA but that as the aneurysm sac dilates this may become turbulent, which in turn may increase shear stress (Asbury *et al* 1995). Whether the pressure acting on the aortic wall is affected by the presence, extent and physical properties of the mural thrombus lining the sac remains to be thoroughly investigated; model studies suggest that intraluminal thrombus may reduce wall stress (Mower *et al* 1997), however, human studies (Schurink *et al* 2000) have failed to support this.

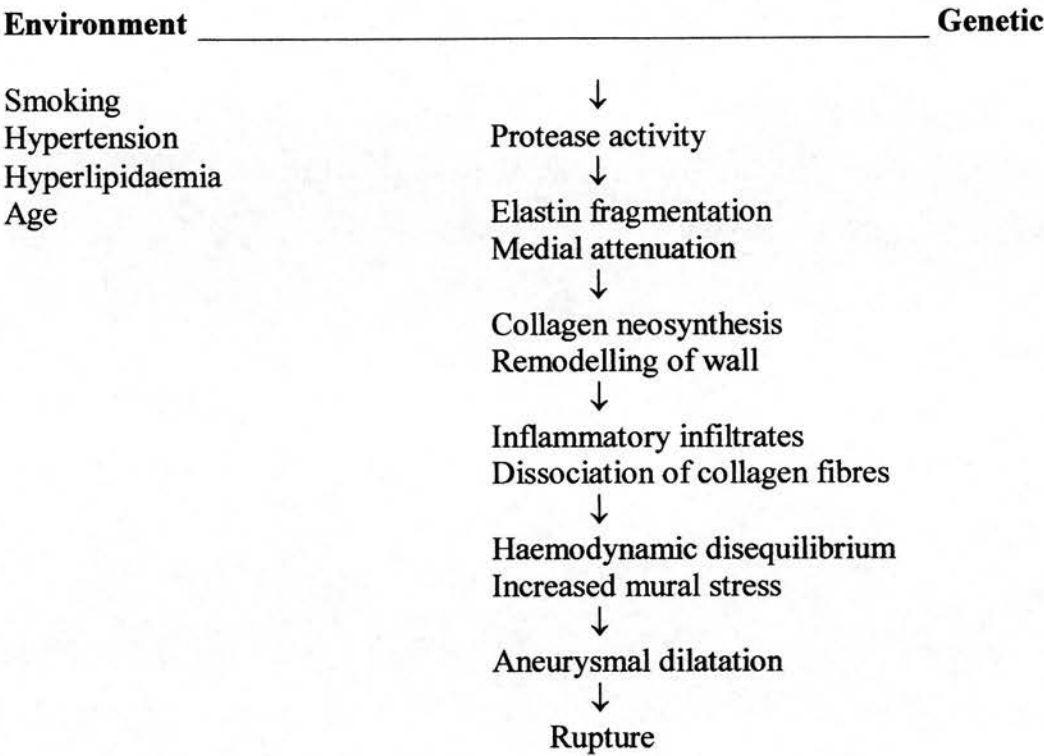
Figure 1.11. Haemodynamic influences in the progression of AAA.



1.4.8 Pathophysiological sequence

The complexity of the process of aneurysm formation is evident. The precise mechanisms behind the proteolytic activity remain to be clarified although the overall sequence of events has become more apparent in recent years (Figure 1.12).

Figure 1.12: Hypothesised pathogenesis of AAA. (Modified from Wilson *et al* 1997)



1.5 Blood Pressure

1.5.1 Definition of normal blood pressure and hypertension

Peak systolic arterial blood pressure is produced by the transmission of left ventricular systolic pressure. Vascular tone and the integrity of the aortic valve maintain diastolic pressure. Normal blood pressure in a resting young adult does not usually exceed 140mmHg in systole or 85mmHg in diastole (Camm 1998). In the elderly, independently of disease, ageing produces rigidity of the vessels that increases systolic pressure to a greater extent than diastolic pressure. In fact, over the age of 65 years, diastolic pressure may even begin to fall (Camm 1998). There is wide variation in 'normal' blood pressure and, indeed, within each individual, BP varies in response to environmental factors such as physical exertion, stress and pain.

Essential hypertension is defined as a sustained high blood pressure not attributable to a specific cause. In recently published guidelines, the British Hypertension Society (Ramsay *et al* 1999) recommended that systolic pressure of ≥ 140 mmHg and diastolic pressure of ≥ 90 mmHg be considered as hypertension.

1.5.2 Pressure measurement

- i. Sphygmomanometry is by far the most acceptable form of measurement to the patient and the easiest for the clinician to carry out. Automated sphygmomanometry is now accepted as a convenient form of measurement since mercury and aneroid manometers require frequent calibration.
- ii. Blood pressure can be measured by inserting a cannula into an artery allowing continuous monitoring. This is the 'gold standard' for BP monitoring. However, it is invasive and therefore not acceptable in the routine follow-up of subjects.

1.5.3 Age and sex differences

Systolic pressure in Western countries increases with age until the sixth decade in females and the seventh decade in males. The relative increase in systolic pressure is greater in males than in females until 25 years of age. Between 45 and 60 years of age, acceleration in the rise of systolic pressure in females leads to female systolic pressure reaching the same level as that in males. Diastolic pressure rises in both sexes until 70 years when it begins to fall (Swales 1996, Starr *et al* 1998).

1.5.4 Hypertension and distensibility

The aorta and other large elastic arteries distend during systole, storing blood volume and potential energy. This energy is released during diastole due to elastic recoil of the arterial wall. The amount of energy stored depends on the degree of distension and the initial diameter of the vessel. The response of the arterial wall to blood pressure is described in terms of its compliance and distensibility (the difference between distensibility and compliance is described in Section 2.5). In established hypertension, distensibility and compliance of the larger elastic arteries is reduced in relation to that of normotensive individuals (Reneman and Hoeks 1995).

1.6 Questions arising from current epidemiological knowledge

It is apparent that the incidence of AAA is rising in Western countries and in spite of major advances in diagnosis, surgical intervention, and anaesthetic technique, the mortality rate for rupture remains unacceptably high. In contrast, elective repair in a specialist unit carries a much lower mortality rate. The question, therefore, is how can rupture be more accurately predicted in order to reduce mortality?

AAA wall degeneration is becoming more clearly understood and it would appear that a non-invasive method of measuring this process might enhance the predictive ability of diameter and expansion rate (the current measures of rupture risk). The use of a non-invasive tool would allow frequent outpatient follow-up. Rupture occurs when the stress within the wall exceeds the tensile strength of the wall material. This is measured by arterial wall compliance and, to a lesser degree, distensibility. Distensibility can be measured non-invasively and so this study aims to test whether non-invasive measurement of AAA wall distensibility provides clinically relevant rupture risk information.

The relationships between AAA diameter, expansion, distensibility and rupture are, at present, not known. This study aims to provide this knowledge by:

- i- describing the range of distensibility in a population of subjects with AAA;
- ii- describing the relationships between distensibility, diameter and rupture.

The haemodynamic relationships between blood pressure, AAA diameter and arterial morphology are complex and no model of this yet exists. It is not possible to measure blood pressure within the AAA non-invasively and so the question arises as to whether brachial pressure could be used instead in the measurement of AAA distensibility.

Atherosclerosis very often occurs in combination with AAA. Although it does not appear to be causally related, the effect of the presence of atherosclerosis on the relationships between blood pressure, diameter and wall distensibility has not been investigated in AAA. This study aims to address the question of whether the presence

of atherosclerosis compromises AAA wall distensibility and consequently affects the risk of rupture.

The specific aims and objectives are listed in Chapter 3.

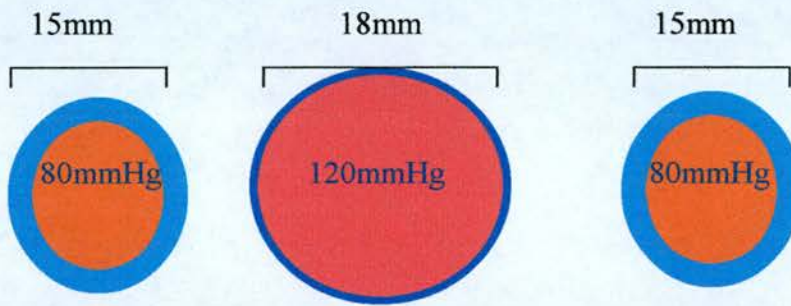
Chapter 2. Physics Background

2.1 Introduction

A description of the pathophysiology of aneurysm formation allows an understanding of aneurysm disease progression. It does not in itself lead to an understanding of the rupture process. As described in section 1.6, this thesis aims to assess the use of arterial wall distensibility in rupture risk assessment. This chapter reviews the physics principles necessary to understand the measurement of the mechanical behaviour of aneurysms undertaken in this study. The areas covered will include consideration of the aneurysm wall properties, of blood pressure and of the principles of the ultrasound instrument that will be used for measurement.

The aorta is a compliant artery: that is, it changes diameter (and length) as a result of changes in blood pressure (Figure 2.1). The principal arterial components determining the compliance of the artery are elastin and collagen (Millis *et al* 1992, MacSweeney *et al* 1994). Their respective roles are discussed in chapter 1.4. Of particular relevance to this thesis is the observation that the elastin/collagen content and concentrations change during AAA growth (He and Roach 1994, White and Mazzaco 1996, Limet *et al* 1998, Sata *et al* 1998), and that the resulting changes in the physical properties of the artery may be crucial in determining whether or not aneurysms grow and/or rupture. The following subsections explain the concept of compliance, distensibility and elasticity, and demonstrate how distensibility can be calculated from changes in the artery diameter and blood pressure.

Figure 2.1. Arterial diameter and wall thickness changes in response to changes in pressure produced by the cardiac cycle. Typical diastolic pressure is 80mmHg: systolic pressure is 120mmHg



2.2 Physical / mechanical properties of aortic wall: definitions

Although this thesis is principally a clinical work, it is necessary to define the physical terms as they are used in this thesis.

Elasticity – The ability of a substance to regain its original form once a deforming force has been removed.

Stress - The force producing the deformation.

Strain - The ratio of the deformation to the original form.

Compliance – The absolute change in arterial volume for a given change in pressure (Reneman *et al* 1996).

Distensibility – The relative change in volume for a given change in pressure (Reneman *et al* 1996).

Pressure-strain elastic modulus – the ratio of stress to strain (Peterson 1960).

Stiffness – The log of the stress: strain ratio that reduces pressure dependence (Hayashi 1980).

Pulse wave velocity – the average speed of the pressure wave travelling along a length of artery not at a localised point.

2.2.1 Stress

Stress (S) is the intensity of a force (F) acting on a given plane and, if it is distributed evenly over a given area (A), is calculated as follows;

$$S = F/A \text{ (Nm}^{-2}\text{)}$$

2.2.2 Strain

Strain is the change in dimension of the artery (diameter, area or volume) under extension (stress). A material in which the change in dimension is uniform in all three directions is said to be isotropic. However, since the elastic properties of the three distinct layers within the arterial wall are different, the arterial wall is anisotropic. The difficulties arising in the measurement of arterial strain have led to the simplified models of stress-strain relations. The relationship between stress and strain is expressed as an elastic modulus.

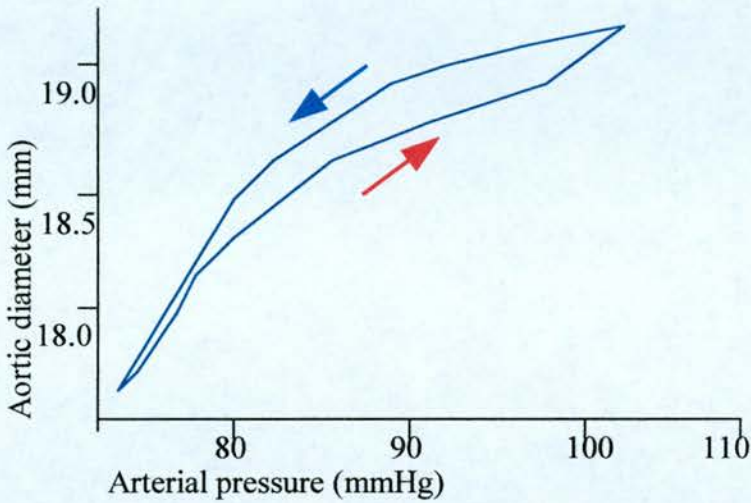
2.3 Indices of Compliance and Distensibility

2.3.1 Young's modulus

The ratio of stress (force per unit area) to strain (fractional deformation) is referred to as Young's modulus (E). For some materials such as steel or rubber, over a limited range of stress, E is constant and is a linear relation. The artery, however, is not homogeneous and

its stress-strain behaviour is not linear (Figure 2.2). The relationship between stress and strain is seen in Figure 2.2 to be curved, with a greater change in diameter at lower pressures. The hysteresis of the pressure-diameter curve is a result of the pressure leading the change in diameter during systole (the upward curve) and the energy being stored and released slowly during diastole (the downward curve). This curve flattens with age. The 'incremental Young's modulus' (Sumner *et al* 1970) refers to the ratio of the change in stress to the change in strain when the curve is non-linear.

Figure 2.2 The hysteresis curve of change in pressure and the resultant change in diameter (modified from Lanne and Bergentz 1995).



2.3.2 Compliance and distensibility

The terms compliance and distensibility are often used interchangeably to describe the generic behaviour of arteries in response to change in blood pressure. However, it is necessary to review the use of different quantities related to the elastic behaviour of arteries, and to specify which quantities and terms will be used in this paper.

The volume of blood within a segment of artery increases as a result of an increase in pressure. The change in dimensions can be expressed by considering the volume change δV , the cross sectional area change δA , or the diameter change δd . The indices that will be discussed are categorised by Hayashi (1980) as the ‘structural stiffness’.

Structural stiffness:– These indices are related to the change in dimensions of the artery wall with a change in pressure. The term *compliance* (C) usually refers to the change in volume (δV) of the blood contained within a segment of artery in which there is a pressure change (δP) i.e. $C = \delta V / \delta P$. The term *distensibility* (D) usually refers to the fractional change in volume for a pressure change (δP) i.e. $D = [\delta V / V] / \delta P$.

In this thesis a variant of the distensibility index has been used. This is called the *pressure-strain elastic modulus*, $E(p)$, and was introduced by Peterson *et al* (1960).

$$E_p = \frac{\delta P}{(\delta d/d)} \quad \rightarrow \quad E_p = K \frac{(P_{\text{systolic}} - P_{\text{diastolic}})}{[(D_{\text{systolic}} - D_{\text{diastolic}}) / D_{\text{diastolic}}]}$$

This term was introduced as a means of comparing arterial data for which the arterial wall thickness is not known (Peterson *et al* 1960). This is applicable in this study as the wall thickness of the AAA cannot be measured using ultrasound imaging. E_p has been used by several workers using ultrasound to measure the elastic behaviour of arteries (Sumner *et al* 1970, Sonesson *et al* 1993). A modification of this term was proposed by Hayashi (1980) in recognition of the fact that the pressure-diameter relationship of arteries is not linear. He introduced the *stiffness* index, (β), which was modified by Kawasaki *et al* (1987).

$$\beta = \frac{\ln(P_{\text{systolic}}/P_{\text{diastolic}})}{[(D_{\text{systolic}} - D_{\text{diastolic}}) / D_{\text{diastolic}}]}$$

The distinction between these indices can be clarified by noting that if the Young's modulus (stress: strain) of the artery remains constant, as the wall thickness increases so the C, D, E_p and β all change in value. As wall thickness increases, C and D

decrease in value while E_p and β increase in value. In this respect E_p and β are both stiffness indices, the inverse of distensibility.

In this thesis the terms 'elasticity' and 'distensibility' are used to describe the generic behaviour of arteries, and the terms 'pressure-strain elastic modulus' and 'stiffness' are used as defined above. The term compliance will not be used. For a more detailed discussion of these concepts the reader is referred to two reviews (Loagun and Gosling 1982, Lanne and Bergentz 1995).

2.3.3 Pulse wave velocity

Pulse wave velocity (PWV) is the velocity with which a pressure pulse is propagated along an artery. It is proportional to the elastic modulus of the arterial wall and can determine the average value of arterial elasticity over a length of the arterial tree. The less elastic an artery is, the higher the PWV (Sumner 1995). Calcification and increased wall thickness also increase PWV. The distance between the sites at which measurements are made determines the length of artery over which distensibility is averaged; for example, to measure the elasticity of the aorta, PWV measurements are taken from the carotid and femoral arteries. However, PWV does not provide an elasticity value for specific points and so for the purpose of this study, has been deemed less useful than the pressure-strain elastic modulus and stiffness in assessing AAA wall distensibility. It is of use in determining the central pressure non-invasively which will be discussed in Chapter 6.

2.4 Blood pressure

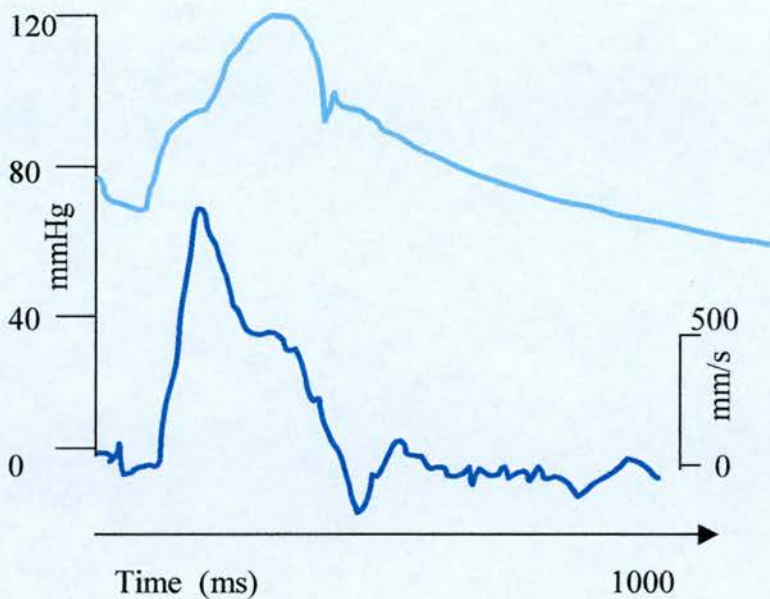
The indices of distensibility used in this thesis require the measurement of the systolic and diastolic blood pressures at the site of the aneurysm. To perform this measurement would require insertion of a pressure transducer into the vessel, which is not justifiable for repeated measurements on patients. Instead measurement of the systolic and diastolic pressure at the brachial artery was performed. Systolic pressure increases along the arterial tree from the aorta to the peripheral arteries by 10-35 mmHg (Nichols and O'Rourke 1998, Pauca *et al* 1992). It was acknowledged that non-invasive measurement of brachial pressure caused a systematic error in the determination of aortic pressure and distensibility (Hansen *et al* 1993). However, that work compared invasive brachial with non-invasive brachial pressures instead of central and brachial pressures. It was also performed on young, non-AAA volunteers. The situation with regard to older patients with AAA had never been investigated. It has become clear that there is a difference between central and peripheral pressure, which in some patients may be of a magnitude that could affect the accuracy of aortic distensibility measured using brachial pressure. To address this problem a recently developed instrument, which enables central pressure to be calculated from non-invasive measurements of peripheral blood pressure, was used. This is discussed in section 2.5.4 of this thesis. The following section describes the physics of blood flow with respect to blood pressure.

2.4.1 Reflected waves

Within the arterial system there are two waveforms relevant to this study; the pressure wave and the flow wave. These waves are reflected wherever there is a discontinuity within the system; branching, changes in wall distensibility, stenoses and dilatations. Nichols and O'Rourke (1998) suggest that the shape of pressure and flow waves are

dramatically different because of reflected waves. It can be seen from Figure 2.3 that the peak of the flow wave occurs at the first dichrotic notch and that pressure continues to rise even after flow begins to decrease.

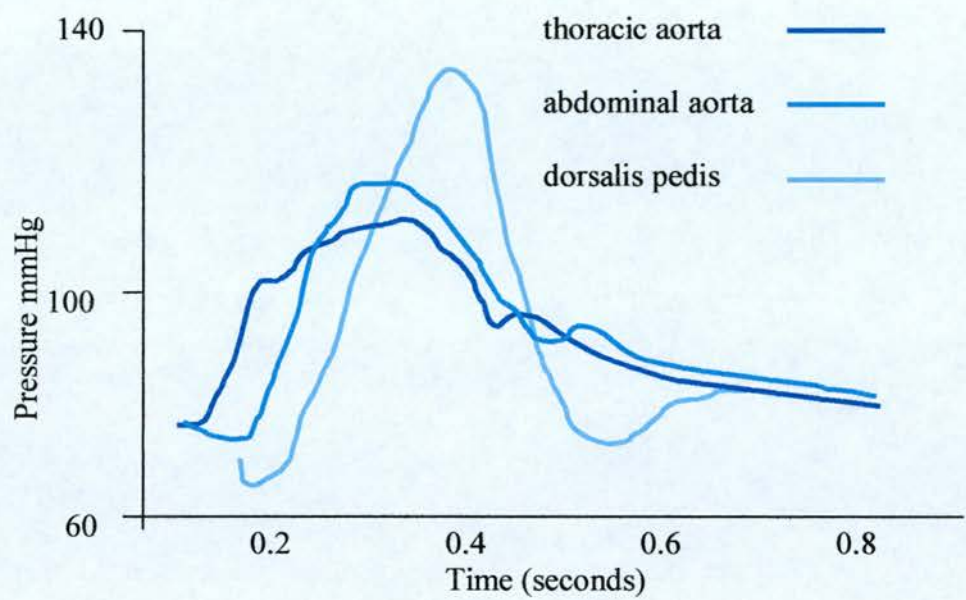
Figure 2.3. Ascending aortic pressure (top) and blood flow velocity (bottom) waves.



A portion of the left ventricular stroke volume is stored in the compliant aorta during systole and then propelled distally by elastic recoil during diastole. When this surge of blood encounters the high resistance imposed by the arterioles, part is transmitted into the capillaries and part is reflected back up the arterial tree. The magnitude of the reflected wave relative to that of the incident (forward going) wave is determined by the peripheral resistance, being greatest when the vascular bed is constricted. As the reflected wave travels back up the artery, it subtracts from the forward flow wave but adds to the

forward pressure wave (Sumner 1995). The result is that the amplitude of the pressure wave increases while that of the flow wave decreases as they travel towards the periphery (Nichols and O'Rourke, 1998). It is the additive effect of reflected waves on the pressure wave that results in systolic amplification and reduced diastolic pressure from central arteries to peripheral arteries (Figure 2.4).

Figure 2.4. Pressure and pulse contours in a normal subject.



2.5 Methods of distensibility and diameter measurement

2.5.1 Available methods of measurement

There are several methods of measuring arterial wall distensibility but this study aimed to look at the aorta in vivo using non-invasive methods. This limited the choice of technique. As discussed above, PWV does not provide information on local arterial distensibility, which was a prerequisite of this study. MRI or ultrasound can be used to measure the fractional change in diameter in response to change in pressure. MRI however, is costly for routine follow-up.

For this study a non-invasive method of measurement of the elastic properties of the aneurysm was needed. B-mode ultrasonography with phase-locked loop echo-tracking software appeared to be the most appropriate method to use. The software could be incorporated within a portable B-mode scanner and it was relatively simple to learn and use on a routine basis. The study subjects were familiar with the ultrasonic component of this technology and it provided a non-invasive method of distensibility and diameter measurement. Previous work reported that the results were reproducible (Hansen *et al* 1993). The equipment is described in detail below.

2.5.2 B-mode ultrasound technology

Ultrasound technology provides detailed cross-sectional images of anatomy visualised in real time. Ultrasound involves the emission of very high frequency sound waves that travel through tissue and are reflected back to the probe. In this thesis, a linear array transducer has been used with the Diamove equipment (section 2.5.3). This type of transducer contains a row of crystal elements which are fired in groups from one side of the transducer to the other allowing the image to be built up line by line (Figure 2.5). The

focused beam of sound transmitted into the tissues is reflected strongly from the boundaries between tissues possessing differing impedance (the speed of sound wave transmission). The depth of the tissue is determined automatically from the time interval between the outgoing ultrasound pulse and the reflected echo. The further away the tissue is, or the more tissue the wave has to travel through, the smaller the reflected wave. The resulting image is a cross-section of the anatomical structures showing the depth and indicating the structure of the differing tissues by means of a grey scale image (Figure 2.6). This is called a 'brightness' mode or B-mode image.

Attenuation increases linearly with the frequency of the waveforms. This means that as the frequency of the sound waves increases so does the attenuation (wavelength decreases). For deep structures this does cause some limitation as there will be a depth beyond which the transducer cannot differentiate between the small, reflected waves and electronic 'noise'. A further difficulty is that the ability to distinguish spatial detail is reduced as frequency decreases. For the required depth, the highest frequency possible is used in order to obtain maximum detail. In the case of the abdominal aorta, the optimal frequency is 3.5MHz. Ultrasonic waves can only travel through fluid so the air gap between the transducer and skin is filled with an aqueous gel.

Figure 2.5. A: A linear array transducer with a beam emerging from a group of elements (crystals) from the right.

B: A second beam from the linear array with the centre axis of the new beam shifted one element to the left.
(Zagzebski 1996)

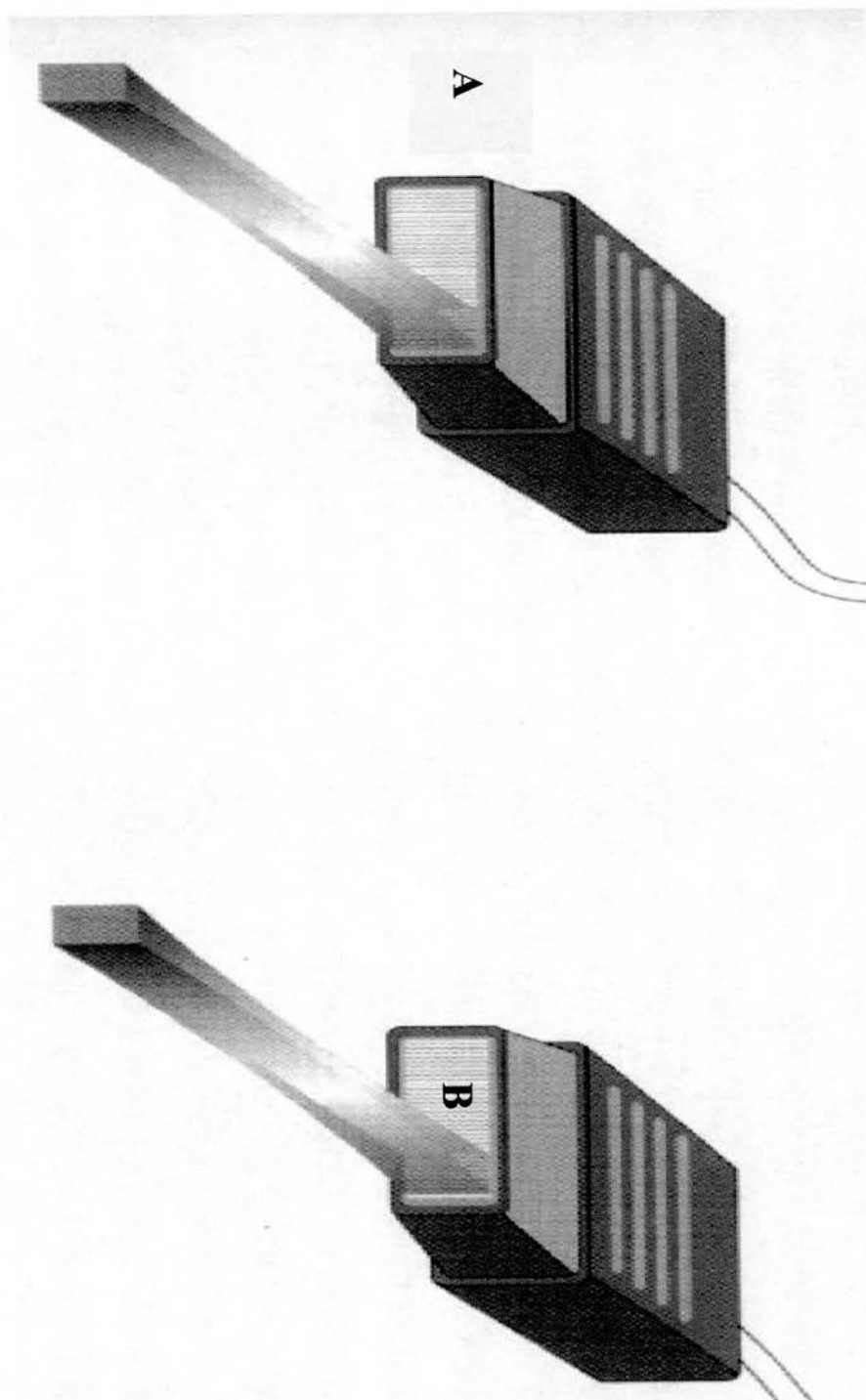
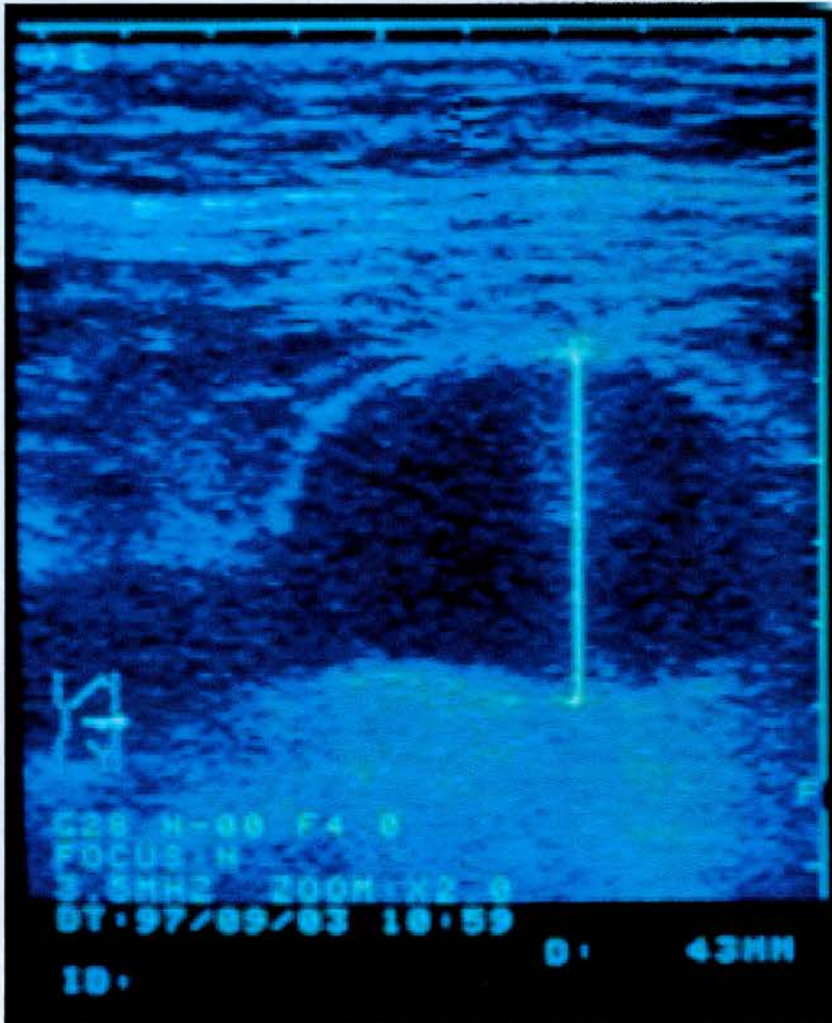


Figure 2.6. Transverse B-mode ultrasound image of the anteroposterior view of a 4.3 cm AAA.



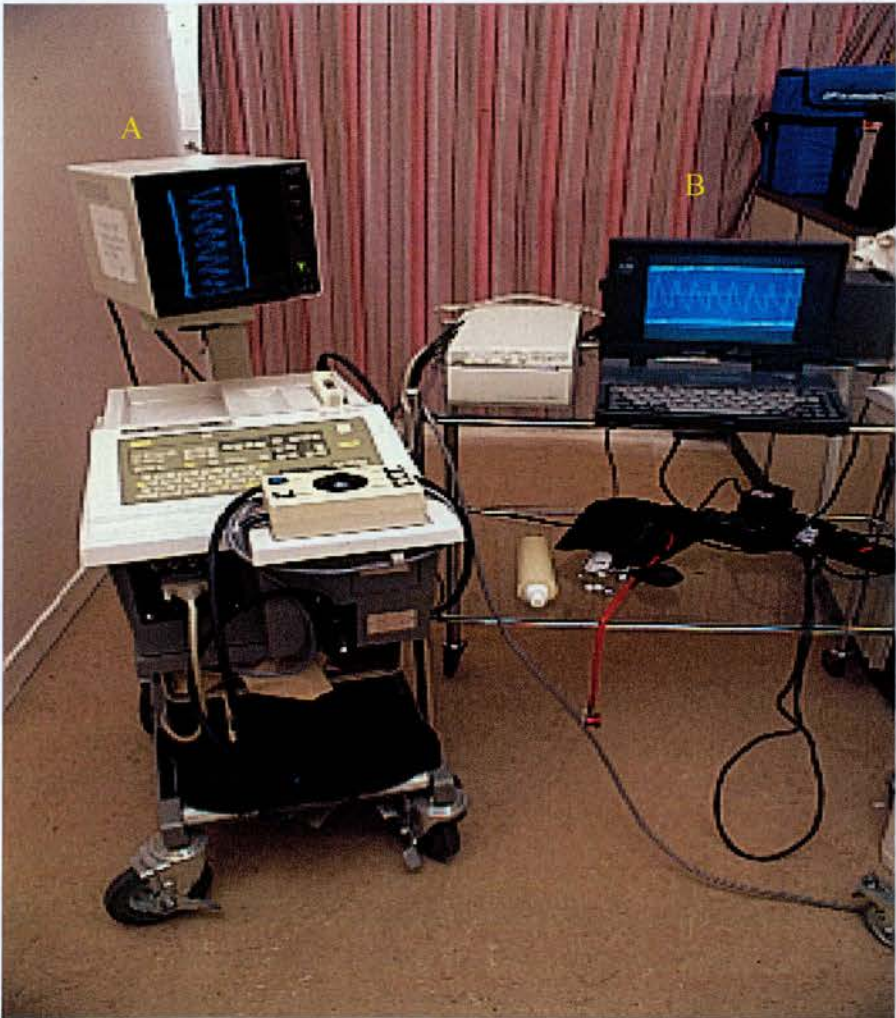
2.5.3 Echo-tracking

The echo-tracking equipment has been used and described previously. (Lanne and Bergentz 1995). An echo-tracking device (Diamove, Teltec AB, Sweden) is interfaced with a B-mode ultrasound scanner (EUB- 240 Hitachi, Japan) (Figure

2.7). A 3.5MHz linear array transducer provides optimal resolution at the depth of the abdominal aorta. An echo-tracking phase-locked loop circuit restores the position of two electronic gates relative to the moving echoes from the anterior and posterior vessel walls. This dual tracking is carried out simultaneously and allows instantaneous calculation of the differences in vessel diameter. The theoretical minimum detectable motion that can be detected is 8 μ m.

Data acquisition and analysis using the Diamove software is carried out by a Pentium 24X personal computer (DCS, Scotland) interfaced with the ultrasonic echo-tracking device. The pressure-diameter curve is registered on the computer in real time and at least three consecutive waves are analysed. This enables the observer to visualise and monitor the quality of the waves as they are being measured (Figure 2.8).

Figure 2.7. The Diamove ultrasonic echo-tracking equipment: A, the ultrasound scanner interfaced with echo-tracking software; and B, the computer with the displaying the pressure diameter waveform produced by the software.



The transducer is placed over the AAA to obtain a longitudinal section; this view allows visualisation of the longitudinal axis of the aneurysm avoiding measurement of oblique angles across the aneurysm which may occur using the transverse view. The anterior and posterior vessel walls are echo-tracked after initial placement of a cursor within the vessel at the point of maximal antero-posterior (AP) diameter (Figure 2.6). The observer controls the length of the cursor to over-ride thrombus or wave refraction noise and lock onto the vessel wall (within the limits of B-mode ultrasonography).

The Diamove software automatically identifies the start and end of each cardiac cycle and using at least three consecutive waves can calculate an average waveform (Figures 2.8 and 2.9). Brachial artery pressure is entered and the software calculates E_p and β using the equations discussed above. The reproducibility of the Diamove equipment and the use of brachial pressure instead of aortic pressure will be discussed more fully in Chapters 5 and 6.

Figure 2.8. The pressure-diameter waveform for an aneurysm over 7 cardiac cycles.

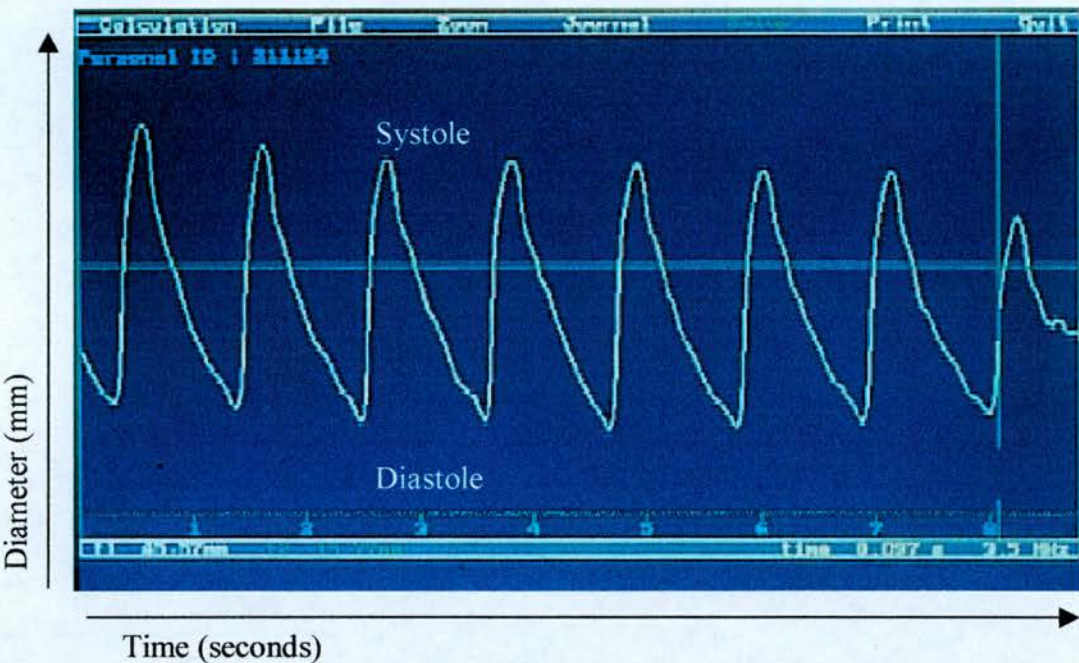
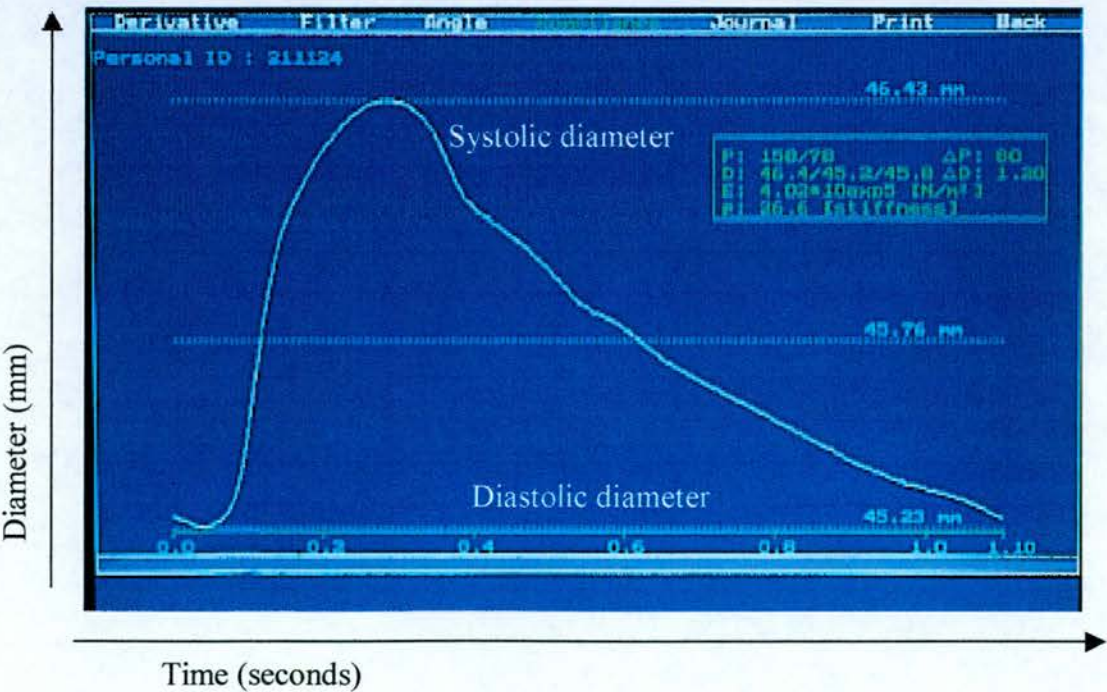


Figure 2.9. The average pressure-diameter waveform from the data collected over 7 cardiac cycles. The insert (top right) shows diastolic and systolic pressure, pulse pressure, minimum, maximum and mean diameter, diameter change, E_p and β .



2.5.3.i Echo-tracking data quality

The quality of the waves in general is determined by the following criteria: the waves are on a level plane; the amplitude of each wave is equal; there are no irregularities in rhythm and the wave has a relatively smooth, dichrotic curve (Figure 2.8). Usable data requires that at least three consecutive waves meet these criteria.

2.5.4 Sphygmocardiography

Sphygmocardiography involves the derivation of the central aortic pressure waveform from recordings of peripheral pulse pressure waveforms. Essentially the peripheral pressure waveform is measured and the central pressure waveform is calculated using a mathematical technique called transfer function analysis. It is not possible to describe this in detail in this thesis but the principles are described in detail by Nichols and O'Rourke (1998).

The pressure waveforms are obtained non-invasively at various peripheral sites using a technique called applanation tonometry. This technique uses a small transducer to flatten the wall of an artery, at which point tangential pressures are eliminated and the sensor is exposed to the pressure within the artery (Figure 2.10).

Figure 2.10. Applanation tonometry uses a tonometer to flatten the arterial wall so eliminating tangential pressures and leaving the transducer exposed to the full extent of intra-arterial pressure.



In order to calibrate peripheral pressure pulse waveforms, the systolic and diastolic pressures are set using brachial sphygmomanometry. When using the radial artery the effect of pressure wave amplification between the brachial and radial arteries is ignored; Nichols and O'Rourke (1998) suggest that only a minimal error results. When measuring from the carotid artery the pressure wave amplification is too great to allow use of the brachial pressure alone. A transfer function is applied in this case.

The software calculates two parameters of the waves' variability allowing the observer to accept the waveform according to pre-stated levels of acceptable

variability; namely wave amplitude >100 mV, standard deviation of systolic and diastolic peak $<5\%$. The validation of the Sphygmocor has been carried out by its developers and found to be acceptable (O'Rourke *et al* 1995). The reproducibility of the SphygmoCor technique in pulse wave analysis and the measurement of central pressure has been assessed independently (Wilkinson *et al* 1998). This technology will be further discussed in Chapter 6.

2.6 Questions arising from physics review

Pressure-strain elastic modulus (E_p) and stiffness (β) index have previously been used to measure arterial distensibility. Ultrasonic echo-tracking has been validated in the measurement of distensibility and a commercially available echo-tracker (Diamove, Teltec, Sweden) was used. However, the variability of this technology has not been tested in AAA subjects, nor has this technology been used to measure diameter in a follow-up setting. This study aimed to test these points in terms of both inter and intra-observer variability. This would also allow recommendations to be made regarding its use as a follow-up tool as well as quantifying the reliability of the data collected.

As discussed in Chapter 1.6, the error involved in using brachial as opposed to central pressure in the derivation of AAA E_p and β will be quantified for the

first time in this study. More specific details of the aims and objectives of this study are given in Chapter 3.

Chapter 3. Aims

3.1 Introduction

Section 1.6 described the gaps in the current knowledge of AAA dynamics, distensibility and rupture risk. Section 2.6 described the gaps in the current understanding of distensibility and its measurement. The following aims and objectives are intended to address these areas:

3.2 Aims

- 3.2.1 To investigate whether data derived from the Diamove ultrasonic echo-tracker are a reproducible method of monitoring AAA expansion and distensibility.
- 3.2.2 To investigate whether AAA wall distensibility is related to rupture risk.

3.3 Objectives

- 3.3.1 To test the variability of the ultrasonic echo-tracking equipment in the measurement of AAA wall diameter and distensibility.
- 3.3.2 To test the effect of using brachial pressure as opposed to derived central pressure in distensibility measurement.

- 3.3.3 To describe the range of values of aortic wall distensibility using E_p and β in a population with AAA of 3.0cm anteroposterior diameter or more.
- 3.3.4 To describe the natural history of AAA wall distensibility, as measured by E_p and β .
- 3.3.5 To test the hypothesis that wall distensibility (E_p and β) is related to risk of rupture of AAA and to describe this relationship.
- 3.3.6 To assess whether smoking, concomitant vascular disease or medication influence AAA size, growth or distensibility.

Chapter 4. Patients and methods

4.1 Introduction

The methodology utilised in the measurement of arterial wall compliance has been discussed in detail in the physics introduction (Chapter 2). The method of patient recruitment, data collection and data analysis will now be discussed.

4.2 Patient recruitment

4.2.1 Numbers

The pilot study data (Appendix III) on diameter and distensibility were not normally distributed and so non-parametric sample size calculations, based on the Mann-Whitney U test (Noether 1987) were carried out. This method required the proportion of ruptures (incidence at 7 months in the pilot study was estimated to be 6%) and the relative risk of rupture (not directly available for distensibility from the pilot study data). A relative risk of rupture of 2 was assumed for maximum diameters greater than the median size when compared with maximum diameters less than the median.

211 patients were required for 90% power, testing at the 5% significance level, to compare differences in maximum diameter between the rupture and the non-rupture groups. This was based on the assumption that 90% of patients

would produce usable data. Because so little was known about distensibility and AAA rupture at the outset of this study, it had to be assumed that differences in distensibility would be apparent between rupture and non-rupture groups.

In retrospect, the anticipated rupture rate was rather high. In this study, 216 subjects were recruited, 210 produced usable data and 28 ruptures occurred. The relative risk of rupture for initial diameters greater than the median was 1.96, which meant that 80% power was achieved. A power calculation was carried out retrospectively for distensibility and found to be 71% at the 5% significance level.

4.2.2 Subjects

Subjects with diagnosed AAA who were attending the vascular outpatient clinic at the Royal Infirmary of Edinburgh under the care of Professor CV Ruckley, Mr JA Murie, Mr AMcL Jenkins and Mr AW Bradbury were invited to participate. Patients were also recruited from:

Ninewells Hospital, Dundee; Mr P McCollum and Mr P Stonebridge
Aberdeen Royal Infirmary; Mr J Engeset and Mr G Cooper
Queen Margaret Hospital, Dunfermline; Ms A Howd
Gartnavel General Hospital, Glasgow; Mr AJ McKay
Freeman Hospital, Newcastle; Mr M Wyatt

Patients with an ultrasound-diagnosed AAA of 3.0 cm or more in antero-posterior diameter were included. It should be noted, however, that the equipment has a variability of 5% in the measurement of static AAA diameter (Hansen *et al* 1993), which resulted in one AAA of 2.9cm at baseline being included. Males and females of any age were invited to attend.

4.3 Follow-up

Follow-up was initially carried out every three months. However, it became apparent that a large number of these elderly subjects were attending several different clinics, often from a considerable distance. The follow-up interval was, therefore, changed to six-months after the study had run for two years.

All subjects were followed up for a minimum of 18 months with the exception of those who died, those whose AAA ruptured or were operated, or those in whom no usable wave could be collected. Details of follow-up are given in Chapter 7.

Patients who were unable to hold their breath for a minimum of 5 seconds or those with any type of cardiac dysrhythmia preventing three consecutive usable waves (see definition in Chapter 2) being produced, were deemed 'unfit' for this study. These patients were recruited to avoid selection bias but were not invited back.

4.4 Data collection

4.4.1 Demographic data

Ethics committee approval was given for this study and informed written consent obtained from each patient prior to commencement. A questionnaire was devised which included standardised World Health Organisation (WHO) questions on claudication, angina and smoking history. Family history of AAA, past medical and drug history were also collected.

At initial assessment the questionnaire was completed. The data collected included:

Measured variables: systolic blood pressure (SBP)

diastolic blood pressure (DBP)

anteroposterior AAA diameter (Dmax)

pulse wave velocity (PWV)

Derived variables:

pulse pressure (PP)	SBP – DBP
mean arterial pressure (MAP)	DBP + 1/3(SBP – DBP)
central pressure	See Chapter 2.5.4
diameter change	Systolic Dmax –Diastolic Dmax
pressure-strain elastic modulus (Ep)	See Chapter 2.3.2
stiffness (β)	See Chapter 2.3.2

Demographics :

age

gender

The Rose/WHO questionnaire (Rose *et al* 1977) and the Edinburgh Claudication Questionnaire (Leng and Fowkes 1992) were used to identify subjects with intermittent claudication and angina (Appendix 1). These questionnaires have been widely recognised as reliable methods of identifying angina and claudication with a high level of sensitivity and specificity (Rose *et al* 1977, Leng and Fowkes 1992). The claudication and angina sections of the combined questionnaire were graded. Grades 1 and 2 were defined as:

Claudication - Grade 1, leg pain does not occur at an ordinary walking pace on the level.

Grade 2, leg pain does occur at an ordinary walking pace on the level.

Angina - Grade 1, chest pain does not occur at an ordinary walking pace on the level.

Grade 2, chest pain occurs at an ordinary walking pace on the level.

Outcome measures - rupture of AAA (RAAA)

emergency operation for rupture

repair of symptomatic AAA

repair of asymptomatic AAA

death from RAAA

death from other causes

This information was collected from medical records and/or death certificates.

Following an outcome event, the patient was no longer followed-up.

4.4.2 Clinical data

The clinical measurement data collected are listed in section 4.4.1. Two recordings of the pressure-diameter wave over 4-11s were collected on each patient, during each session, with brachial artery pressure measured each time.

The 'best' of the two pressure-diameter traces was selected for analysis on the basis of the following criteria:

- 1) The maximum diameter measurements were within 2mm of the estimated value (estimated diameter being taken from a static image of systolic diameter), or 5% if the aneurysm was less than 4cm wide;
- 2) At least three consecutive cardiac cycles producing uniform waves were available for analysis;
- 3) Any obvious arrhythmias were excluded.

4.4.3 Blood pressure measurement

Measurement was carried out with the patient in the supine position with the arm resting horizontally on the bed at the patient's side. Blood pressure was measured from the brachial artery in the right arm (Fowkes *et al* 1991) using, initially, a hand held sphygmomanometer (years 1 and 2 of the study) and subsequently an automated sphygmomanometer (model 711, Omron Healthcare GmbH, Hamburg) (Figure 4.1) (years 3-5). The cuff was wrapped around the upper arm and inflated until the brachial artery was occluded. Systolic pressure was taken as the pressure where the first Korotkoff sounds (phase 1) were detected while cuff pressure was reduced. Diastolic pressure was taken as the pressure where the final Korotkoff sounds (phase 5) disappeared (Camm *et al* 1998).

Figure 4.1. Blood pressure measurement from the brachial artery using an automated sphygmomanometer.



Hypertension: Although the questionnaire collected information on treatment for hypertension, this was not used in the analysis to define the presence of hypertension. A separate variable recording the presence of hypertension at each follow-up was derived from measured blood pressure data according to the definition (Ramsay *et al* 1999): diastolic BP \geq 90mmHg, systolic BP \geq 140mmHg.

4.5 Data collection failure

The patient was not invited back if they were deemed too frail to attend (e.g. unable to mobilise onto the bed or dementia prevented complete understanding of the visit). However, if they were fit enough to attend but were unable to produce usable data, they were invited back because correct use of the equipment requires a degree of practice/expertise. It was thought that for some subjects, anxiety regarding the examination and extraneous circumstances on the day of appointment might have affected compliance data collection. If no data were collected at two consecutive appointments it was deemed unnecessary to invite the patient back.

Family and drug history data could not be collected in two subjects because of dysphasia and poor memory. In 10 subjects, the angina data was deemed 'missing' according to the Rose/WHO (Rose *et al* 1977) guidelines because the subjects could not answer question 12.07 (Appendix 1) on the location of chest pain. Claudication status could not be evaluated because 5 subjects did not walk or exercise in a way that would have elicited the symptoms used by the questionnaire.

Measurement of the mechanical properties of the aorta *in vivo* was problematic for several reasons:

- 1) The position of the aorta deep within the abdominal cavity makes visualisation difficult, especially in overweight subjects.

- 2) The aorta cannot be palpated as easily as a more peripheral artery, for example the femoral artery.
- 3) As the main arterial route from the heart, it is not easily possible to excise the aorta or insert probes inside it without potentially serious side effects.
- 4) Palpation and visualisation of the aorta may require a degree of pressure to be applied to the probe especially in the overweight subject. However, the examination procedure should not exert any pressure upon the arterial wall because this may limit wall movement.

4.6 Data analysis

All clinical measurement data with the exception of age, were found to be skewed, so non-parametric statistical tests have been used. The skewed data were logarithmically transformed to the natural log when there was no non-parametric test available. Data analysis was carried out using SAS 6.12 and SPSS version 10 (SPSS® 1999, SAS/STAT 1988). Statistical guidance was provided by Ms AJ Lee of the Medical Statistics Unit, and Dr AJ Lee of the Wolfson Unit for the Prevention of Peripheral Vascular Disease, University of Edinburgh. The Cox proportional hazard model was carried out by Ms AJ Lee.

4.6.1 Univariate analyses

Univariate analyses involved the following methods:

- Mann-Whitney U test for the comparison of two independent groups.
- Kruskal-Wallis test for the comparison of more than two independent groups.
- Spearman's rank correlation for the measure of association between two variables.
- Wilcoxon's signed rank test for the comparison of paired data.

4.6.2 Cox proportional hazard model and survival analyses

Since the univariate analyses showed few significant relationships between baseline or final follow-up distensibility and risk of rupture, it was possible that the absolute value of E_p and β was less important than the relative change in either variable over time. To investigate whether a marked change in distensibility occurred prior to rupture, the statistical models had to take account of changes in each variable over time. The Cox proportional hazard model took account of time-dependent changes in the variables.

Multivariate analysis (Cox proportional hazard model) also enables investigation of the effect of each variable in relation to the effects of the other variables, i.e. one variable could be adjusted for all the other variables. The main aim of this study was to discover whether E_p and β had a significant impact on risk of rupture. There were five possible outcomes: 1) rupture with

no attempted repair, 2) elective, asymptomatic surgical repair, 3) emergency or symptomatic repair, 4) intact AAA (patients were alive and had intact AAA by the end of the study) and 5) death from other causes. Sections 4.4.1 and 2 show that there were a large number of time-dependent and non time-dependent variables which may impact upon these outcomes

The Cox proportional hazard model is a commonly used survival analysis method, which is similar to multiple regression. It allows the assessment of the effect of several independent variables (age, sex, blood pressure, diameter, distensibility, risk factors, co-morbidity, smoking and drug history) on a dependent variable (time to rupture). While other survival analysis methods assume a parametric distribution for survival time, the Cox proportional hazard model does not assume any particular distribution and so has been chosen for these, mostly non-parametric, data. The details of the Cox model will be described more fully in Chapter 11, where the results of this analysis are presented.

Within the rupture group, the time from baseline to rupture varied widely. To assess the characteristics of the rupture group, 'time to rupture' was used as the dependent variable in the multivariate analyses and can be interpreted as risk of rupture at any given point in time. This type of survival analysis uses 'time to an event' as the dependent variable, so-called because often the event of importance is death. However, the 'event' of interest does not need to be

death and in this analysis was rupture. It is also the case in survival analysis that many patients do not undergo the 'event' by the end of the study. Other multivariate methods of survival analysis would exclude this data. However, these subjects contribute important information to this study since they have not ruptured within time (t), the length of the study, and so the Cox model uses these data.

Chapter 5. Variability of the measurements derived using the Ultrasonic Echotracker

5.1 Introduction

Measurement of aortic distensibility using an echo-tracking device (Diamove, Teltec AB, Sweden) is reproducible in healthy, non-aneurysmal subjects (Hansen *et al* 1993). However, this may not be true in patients with AAA because of cardiorespiratory co-morbidity, obesity and variable aneurysm morphology. Before the relationship between aortic distensibility, future growth and rupture can be investigated, it is essential to quantify the reproducibility of this method.

5.2 Aims

The aim of this study, therefore, was to examine for the first time, the intra- and inter-observer variability associated with the commercial ultrasonic phase-locked echo tracker used in the measurement of AAA distensibility.

5.3 Additional methodology

The use of the echo-tracking ultrasound system has been discussed in detail in Chapter 2.5.3 and 4.4, the blood pressure technique has been discussed in Chapter 4.4.

Observer A underwent 5 months of training in the Departments of Radiology and Vascular Surgery at the University of Edinburgh. Observer B received two months of training in the Department of Vascular Surgery at the University of Edinburgh prior to commencing the study. Observers were blind to Dmax, Ep and β as these variables were only shown on the computer screen once analysis had been carried out at the end of the study. The observers examined each patient alone and so were blinded to each other's blood pressure measurements.

5.3.1 Data collection

Study 1:- Intra-observer variability

Observer A performed two sets of AAA distensibility measurements during two sessions 30-60 minutes apart, on each of 14 patients during a single visit to the Vascular Studies Unit (VSU).

Study 2:- Inter-observer variability

Observers A and B performed two AAA distensibility measurements on a further 23 patients during each of two visits to the VSU two weeks apart.

5.3.2 Statistical methods

Data were analysed using the statistical package SPSS-X (SPSS-X 1986). Statistical advice was provided by Dr AJ Lee. Medians of the variables in

studies 1 and 2 were compared using the Wilcoxon signed rank test to check for systematic bias between the sessions and observers. The coefficient of variation expresses the standard deviation (SD) of a single set of measurements as a percentage of the sample mean. However, in this study, the aim was to express the degree of variability between two sets of measured data. For that reason Bland and Altman's (1986) coefficient of variation of method error (CVME) was used.

5.4 Results

5.4.1 Study 1: Intra-observer variability

Table 5.1 shows the median and interquartile range of the variables measured by observer A during sessions 1 and 2. There were no statistically significant differences between the first and second sessions with regard to the distributions of any of the distensibility measurements (Figure 5.1). The intra-observer CVME for observer A's measurements were low for the directly measured variables: systolic BP 7.3%, diastolic BP 5.4% and Dmax 2.6%. The intra-observer CVME of the derived variables were higher: Ep 21.2%, β 17.6% and diameter change (Dch) 18.2%. Figures 5.2 and 5.3 show the Bland-Altman plots of the intra-observer differences in Ep and β measured by observer A.

Figure 5.1. Intra-observer differences for diameter and distensibility measurement.

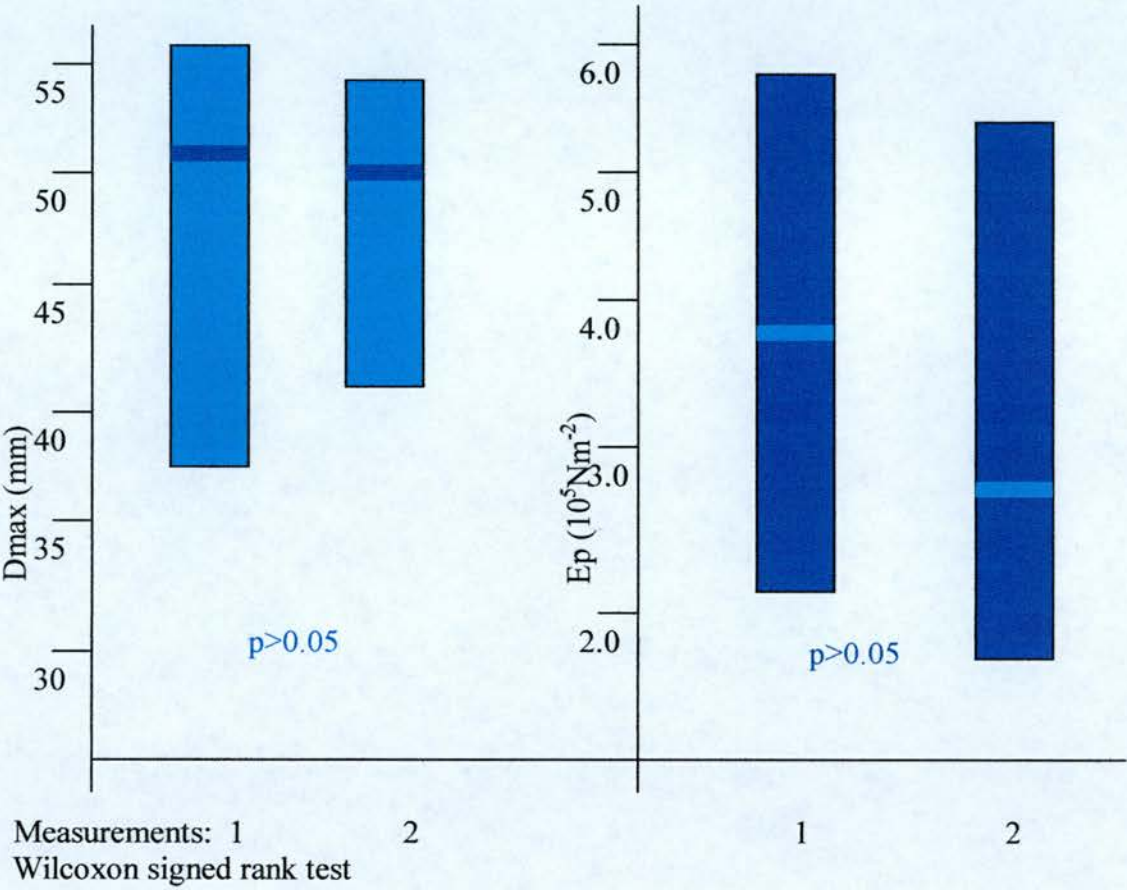


Figure 5.2. Bland and Altman plot of intra-observer differences in E_p measured by observer A at two sessions 30 –60 minutes apart.

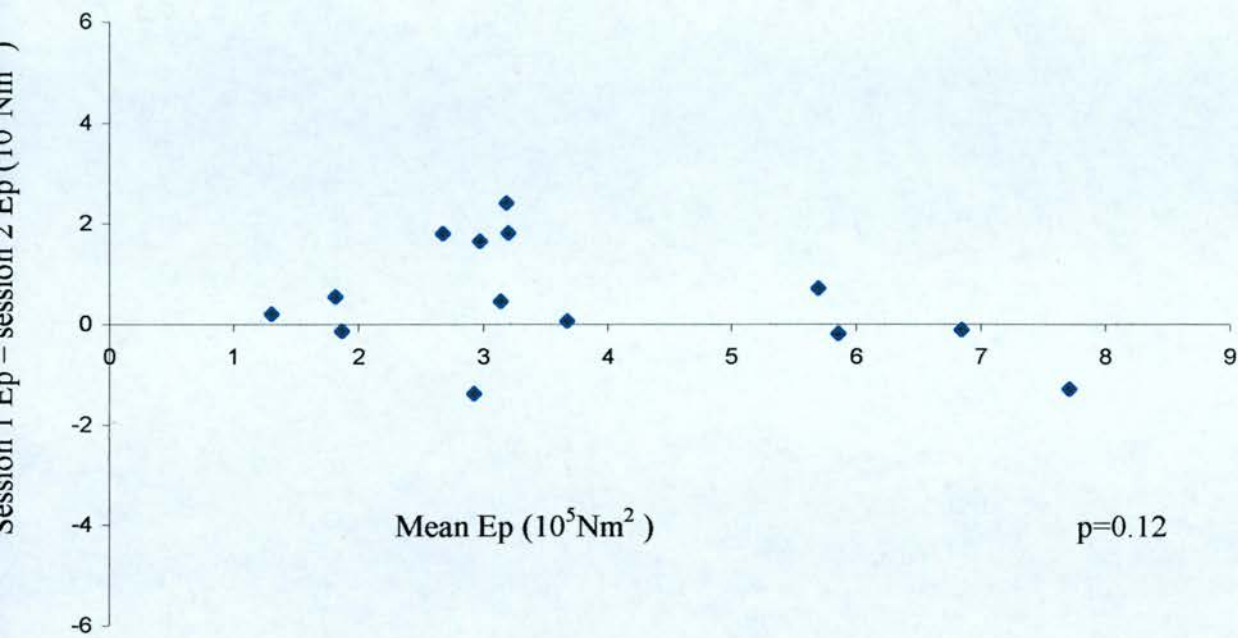
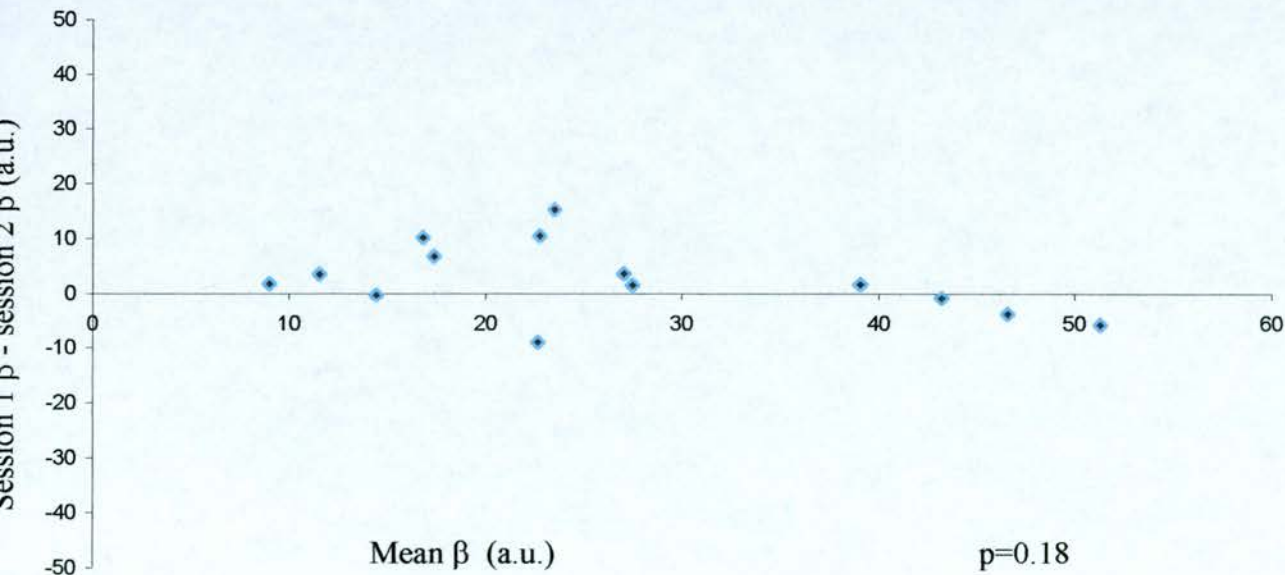


Figure 5.3. Bland-Altman plot of intra-observer differences in β measured by observer A at two sessions 30-60 minutes apart.



5.4.2 Study 2: Inter-observer variability

Table 5.2 shows the median and interquartile range of each variable obtained by observers A and B at each visit. Significant inter-observer differences were only found with regard to Dmax at visit 1 ($p \leq 0.05$) and diastolic BP at visit 2 ($p \leq 0.05$). Figures 5.4 and 5.5 show the Bland and Altman plots of the inter-observer differences in Ep and β at visit 1.

Figure 5.4. Bland-Altman plot of the inter-observer difference in E_p between observers A and B at visit 1.

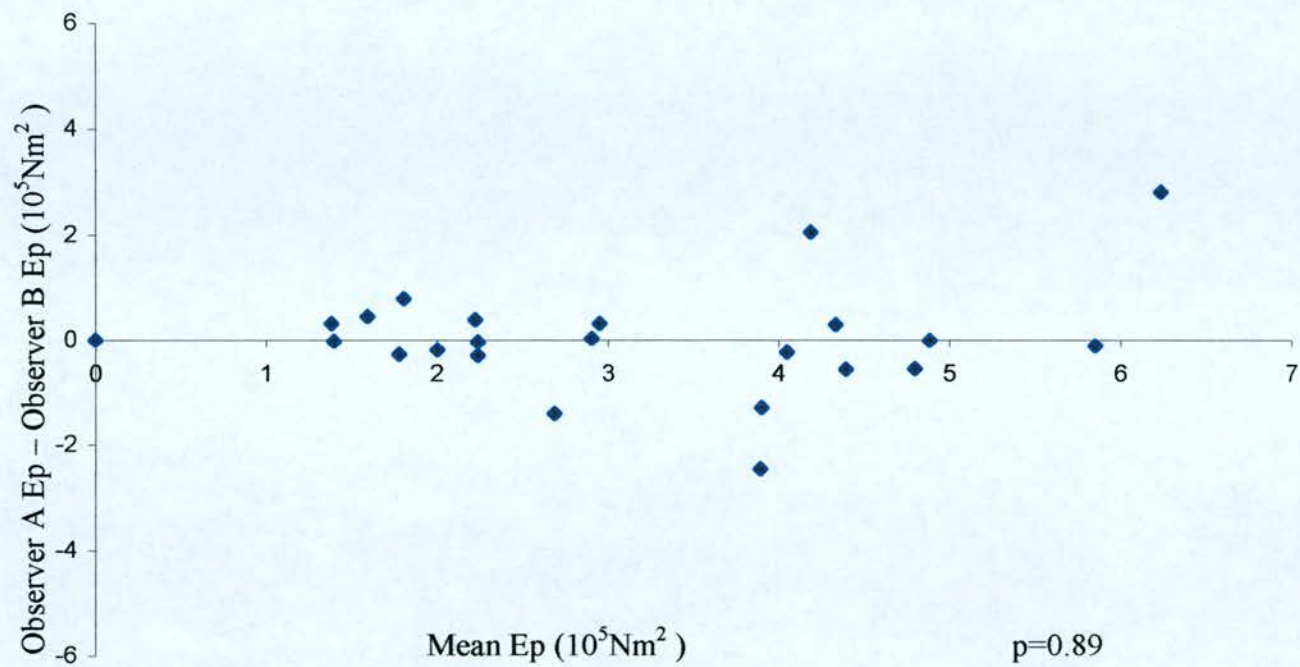


Figure 5.4. Bland-Altman plot of the inter-observer difference in β between observers A and B at visit 1.

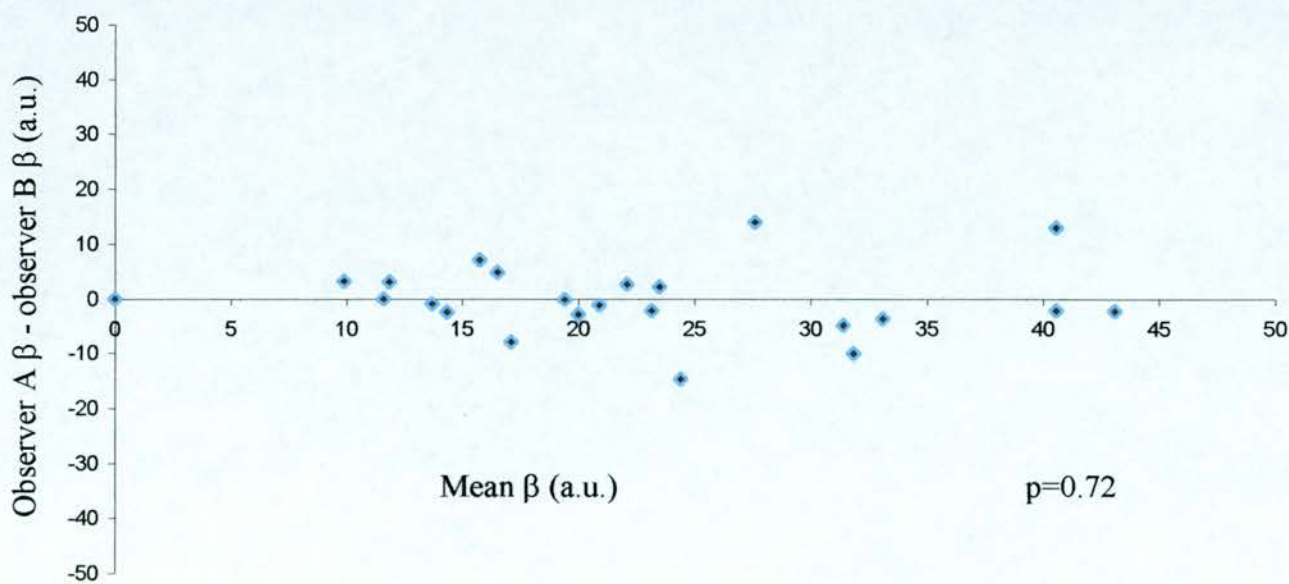


Table 5.1. Study 1: Intra-observer variability in the measurement of AAA wall distensibility and brachial artery blood pressure made by observer A on two sessions 30-60 minutes apart (n=14).

Variables	Session 1			Session 2		
	<u>median</u>	<u>IQR</u>	<u>Range</u>	<u>median</u>	<u>IQR</u>	<u>Range</u>
DBP (mmHg)	81	72-83	58-98	77	70-88	58-93
SBP (mmHg)	140	126-160	122-186	138	123-148	116-184
PP (mmHg)	60	56-73	41-108	62	43-67	36-113
Dmax (mm)	51	38-56	31-68	50	41-54	31-69
Ep (10 ⁵ Nm ⁻²)	3.75	2.2-5.8	1.4-7.1	2.6	1.9-5.5	1.2-8.4
β (a.u.)	28.08	17.18-40.56	9.85-48.40	21.43	13.5-39.66	8.2-54.25

Wilcoxon signed rank tests for differences between sessions were all non-significant (p>0.05)

All variables reached a high ($r > 0.5$) and significant ($p \leq 0.05$) degree of intra- and inter-observer correlation (Table 5.3). Intra- and inter-observer measurement of Dmax demonstrated a significant degree of correlation ($r \geq 0.96$ and $r \geq 0.94$ respectively). CVME for intra- and inter-observer variation was $\leq 10\%$ for the variables directly measured by the observers (diastolic BP, systolic BP and Dmax) and $\leq 35\%$ for the mathematically derived parameters (pulse pressure, E_p , β) (Table 5.4). However, CVME is a parametric test and none of these data were normally distributed. To address this, the values were subsequently log transformed before calculating the CVME. For example; β in Table 5.4 became; for observer A 10.2%; observer B 8.6%; visit 1 6.6%; visit 2 10.2%. This is not the correct usage of this parametric test and so we have only calculated β to show the potential effect of skewness on CVME

Table 5.3. Median and interquartile range of variables obtained at two sessions by two observers, and Spearman's rank correlation coefficients (r) for intra and inter-observer measurements of parameters in study 2

Variables	a. intra-observer correlation		b. inter-observer correlation		
	Median (IQR)	Observer A	Observer B	Visit 1	Visit 2
DBP (mmHg)	78 (70-84)	r=0.81 ***	r=0.78 ***	r=0.87 ***	r=0.82 ***
SBP (mmHg)	140 (123-153)	r=0.62 ***	r=0.81 ***	r=0.85 ***	r=0.72 ***
PP (mmHg)	58 (50-73)	r=0.50 *	r=0.83 ***	r=0.84 ***	r=0.56 **
Dmax (mm)	51.6 (45-55)	r=0.98 ***	r=0.96 ***	r=0.95 ***	r=0.94 ***
Ep (10 ⁵ Nm ⁻²)	3.1 (2.1-4.6)	r=0.64 **	r=0.62 **	r=0.82 ***	r=0.66 ***
β (a.u.)	22.3 (15.5-32.6)	r=0.71 ***	r=0.68 ***	r=0.77 ***	r=0.74 ***

NB Diameter change is that during each cardiac cycle.

*p≤0.05, **p≤0.01, ***p≤0.001.

Table 5.4. Coefficients of variation of method error (CVME) between intra (a) and inter-observer (b) measurements of blood pressure, aortic diameter and diameter change, elasticity and stiffness from study 2.

Variables	a. intra-observer		b. inter-observer	
	Observer A	Observer B	Visit 1	Visit 2
DBP (mmHg)	7.0%	7.8%	5.7%	5.9%
SBP (mmHg)	10.0%	8.5%	5.1%	7.9%
PP (mmHg)	23.0%	13.4%	11.9%	20.0%
Dmax (mm)	2.2%	3.5%	2.2%	3.5%
Ep (10^5Nm^{-2})	35.3%	26.0%	23.1%	32.7%
β (a.u.)	32.0%	25.6%	21.2%	29.4%

Table 5.5. Comparison of coefficients of variation of method error (CVME) of distensibility variables between different studies of

AAA and non-AAA subjects.

Authors	No. of subjects	Vessel	SBP	DBP	Dmax	Diameter change	Ep	β
Hansen et al (1993)	8F	normal	2%	3%	5%	16%	21%	23%
Lanne et al (1992)	4M	normal	-	-	-	-	6%*	6%*
Wilson et al (present study)	14 F&M	AAA	7%	5%	3%	18%	21%	18%
F-female, M-male								

*Standard deviations quoted in this study

5.5 Summary

- There were no significant differences in intra-observer measurement of any of the variables.
- There were no significant and consistent differences in inter-observer measurement of any of the variables (diastolic BP differed at visit 2 but not visit 1 and Dmax at visit 1 but not 2), the Bland –Altman plots reflect these findings.
- Intra- and inter-observer CVME for directly measured variables were low ($\leq 10\%$) while CVME for the derived variables were higher ($\leq 21\%$ for observer A, study 1).
- The CVME is a parametric test. However, when these skewed data were logarithmically transformed to normality, intra-observer CVME for β was 10.2% and 8.6% for observers A and B respectively.

5.6 Discussion

There were no statistically significant differences in intra-observer measurement of any of the distensibility variables. Significant inter-observer differences were only found in DBP at visit 2 and Dmax at visit 1. Intra- and inter-observer CVME for directly measured variables were low ($\leq 10\%$) while CVME for the derived variables were higher ($\leq 21\%$ for observer A in study 1 but up to 35% in study 2).

Variability of the Diamove echo-tracking device has not previously been reported in patients with AAA. However, present data were comparable with those obtained in a previous methodological study (Hansen *et al* 1993) using healthy subjects with normal aortas (Table 5.5). A third study also investigated aortic distensibility in 4 young (age ≤ 35 years), non-aneurysmal subjects (Lanne *et al* 1992) and reported on 4

distensibility measurements from each subject during one visit. These authors (Lanne *et al* 1992) expressed their methodological error for E_p and β in terms of SD. SD was not appropriate for the analysis of this group of AAA subjects because distensibility measurements were not normally distributed and were highly variable. Lanne *et al*'s (1992) results were, therefore, less comparable with the present findings than those of Hansen *et al* (1993). The present study was also unique in that measurements were taken in two distinct sessions up to 2 weeks apart.

Blood pressure and maximum aortic diameter were the two variables directly measured by the observers and, therefore, the only variables that were prone to observer bias. The low CVME for these variables indicated that this echo-tracking equipment could be reliably used in the follow-up of AAA maximal diameter. There may, however, have been some random error in the values calculated for E_p and β because these are derived values and were not directly measured. The use of brachial artery pressure rather than central aortic pressure is likely to have biased calculation of E_p and β and this will be discussed in Chapter 6. However, the error will have been systematic, affecting all patients approximately equally. Invasive measurement of aortic pressure is not practicable for routine distensibility follow-up. Most previous studies using Doppler phase-locked loop echo-tracking have assumed that brachial blood pressure is consistently related to aortic pressure (Hayashi 1980, Hansen *et al* 1993, Lehmann *et al* 1993, Lanne *et al* 1992).

The high CVME of both E_p and β must be viewed in the context of the wide range of distensibility observed in this particular study group (Table 5.1). For example, E_p varied by a factor of 12.75 (0.74 to $9.44 \times 10^5 \text{Nm}^{-2}$) and β varied by a factor of 12.0

(5.6 to 66.8 a.u.). It should also be noted that, with the exception of blood pressure, the variables measured were all skewed to the right. Because there is no non-parametric equivalent of the CVME, the effect of this skewness on the values of CVME cannot be ascertained. However, if a logarithmic transformation had been applied to the data before the CVME was calculated, the resultant CVME would have been substantially reduced. For example, the non-transformed CVME for observer A's intra-observer stiffness was 32% and for observer B, 25.6%. After transformation these CVME were 10.2% and 8.6% respectively. Using the CVME calculated from transformed data does not allow direct comparison of variability with previous studies. However, it does suggest that the Bland and Altman (1986) test for CVME is not applicable to skewed data. More importantly for this study, it also suggests that the high level of variation was in fact due to the large variation of E_p and β within the study population rather than due to the technique. The diameter and distensibility variations, which were observed between visits in study 2, may also have reflected a certain degree of real variation in AAA wall distensibility over time.

When the raw data were examined, there were two particular subjects in whom markedly different diameters were measured. These patients were difficult to scan because of obesity and cardiorespiratory disease. These subjects were not removed from the study because it would have biased assessment of reproducibility. Nevertheless, approximately 10% of subjects could not be satisfactorily scanned because of the factors mentioned above. Excluding such patients would have increased the apparent reproducibility of the technique.

The longitudinal view of the AAA allowed a true anteroposterior measurement to be made perpendicular to the long axis of the aneurysm. Three distensibility measurements were made at each examination. Each was slightly different due to slightly differing blood pressure and due to the cursors inevitably locking onto different layers of the wall. Slight changes in the angle of the probe may also have increased the variability of diameter change but this was not investigated specifically in this study.

The echo-tracking technique involves placing the cursors onto the echoes of the anterior and posterior walls while the vessel wall is moving with each cardiac cycle. Tracking of the same points within the wall structure is difficult because the quality of the B-mode imaging does not allow easy differentiation between thrombus, calcification, intima and media. It is likely that improvement in the image quality and echo-tracking technology will reduce the effect of these factors on reproducibility.

The learning curve associated with echo-tracking distensibility measurement was steep for observer A who had no previous experience of ultrasonic scanning. However, intensive training by radiology staff in the recognition of abdominal structures and variations in AAA wall morphology meant that the curve levelled off after about three months. At this point the observer A's measurements were within 2mm of those reported by the ultrasound department. Observer B was subsequently taught the technique by observer A. This may have introduced some systematic bias into the study, although observer B had previous experience scanning AAA so reducing the learning curve considerably. At the time of the study, observer A had two years of experience with the equipment while observer B had three months

experience. It was not possible to provide a longer training period. This may also have contributed to the intra-observer CVME (Table 5.4).

There are many factors that might influence AAA distensibility, for example blood pressure, AAA geometry and thrombus content. As such, it is perhaps unsurprising that the CVME were high. However, the following selection criteria can be used to minimise variability:- 1) the maximum diameter measurements should be within 2mm of the estimated value, or 5% if the aneurysm is less than 4 cm wide; 2) at least three consecutive cardiac cycles producing uniform waves should be selected for analysis and; 3) obvious arrhythmias should be excluded. It is recommended that both intra- and inter-observer variability should be measured, albeit in a small number of subjects, in any study of distensibility. Variability should be reassessed regularly.

5.7 Conclusions

These results suggest that the Diamove echo-tracking technique is a reliable method of measuring AAA diameter (to within 2-3.5% of the 'true' value), and pulsatile diameter change enabling calculation of E_p and β . The clinical utility of these variables will be investigated in rest of this thesis.

Chapter 6. Use of derived central pressure in the measurement of aortic distensibility

6.1 Introduction

Poiseuille's law states that blood flow is directly proportional to the difference between inflow (aortic) and outflow (peripheral) pressures (Berne and Levy, 1998). Systolic pressure increases along the arterial tree from the aorta to the peripheral arteries by 10-35 mmHg (Kroeker and Wood 1955, Rowell *et al* 1968, Pauca *et al* 1992) due to wave reflections and differences in vessel stiffness. In contrast, diastolic pressure and mean arterial pressure (MAP) fall by approximately 2mmHg (Kroeker and Wood 1955, Rowell *et al* 1968, Pauca *et al* 1992), thus providing the pressure gradient for forward flow of blood. The net result is an increase in pulse pressure towards the periphery. Use of brachial pressure as opposed to intra-AAA pressure may alter the value obtained for distensibility by the Diamove system. Intra-aortic pressure cannot be measured non-invasively and so a non-invasive technique for deriving central pressure has been used to examine the effect of using brachial pressure.

6.2 Aims

The aim of this study, therefore, was to compare AAA distensibility (E_p and β) obtained using brachial BP with that calculated from derived central BP (estimated by pulse wave analysis).

6.3 Additional methodology

Central blood pressure may be estimated by means of pulse wave analysis (PWA, Sphygmocor, SCOR; PWV Medical, Sydney, Australia) (O'Rourke and Gallagher 1996). Briefly, PWA uses a generalised transfer function (GTF) to convert a peripheral arterial pressure waveform into a central (ascending aortic) arterial pressure waveform and to calculate the augmentation index. Peripheral waveforms are recorded with high fidelity by applanation tonometry. When the opposing external curved surfaces of a vessel are flattened (applanated) by a tonometer until parallel, the contact pressure between the two equals the intra-arterial pressure (Chapter 2, Figure 2.10). The validation of sphygmocor will be discussed in more detail in Section 6.6.

An oscillometric pressure monitor (model 711, Omron Healthcare GmbH, Hamburg) was used to measure right brachial pressure, and the Diamove to measure aortic E_p and β , in 28 subjects (18 male, 10 female). PWA (SphygmoCor) was measured in the right radial artery using a high fidelity micromanometer (SPC-301, Millar Instruments, Texas, USA) (Wilkinson *et al* 1998a). After 20 sequential waveforms were collected, an averaged peripheral and corresponding central waveform was generated (O'Rourke 1995).

The software calculates two parameters of the waves' variability, allowing the observer to accept the waveform according to pre-stated levels of acceptable variability; namely, wave amplitude >100 mV and the standard deviation of systolic and diastolic peak $<5\%$. The reproducibility of the SphygmoCor technique in pulse wave analysis and the measurement of central pressure has been evaluated previously (Wilkinson *et al* 1998a). Wilkinson *et al* (1998a) concluded that applanation

tonometry using the radial artery produced clinically reproducible results and was, in fact, more reproducible than some automated sphygmomanometers.

Distensibility, calculated as described in Chapter 2 using derived central pressure, is referred to as Ep^c and β^c . Distensibility calculated using brachial pressure is referred to as Ep^b and β^b . Statistical analysis was carried out using SPSS 8.0 (SPSS 8.0 1998).

Bland and Altman plots were used to measure the level of agreement between the two methods of blood pressure measurement because neither method is the gold standard for aortic pressure measurement.

6.4 Results

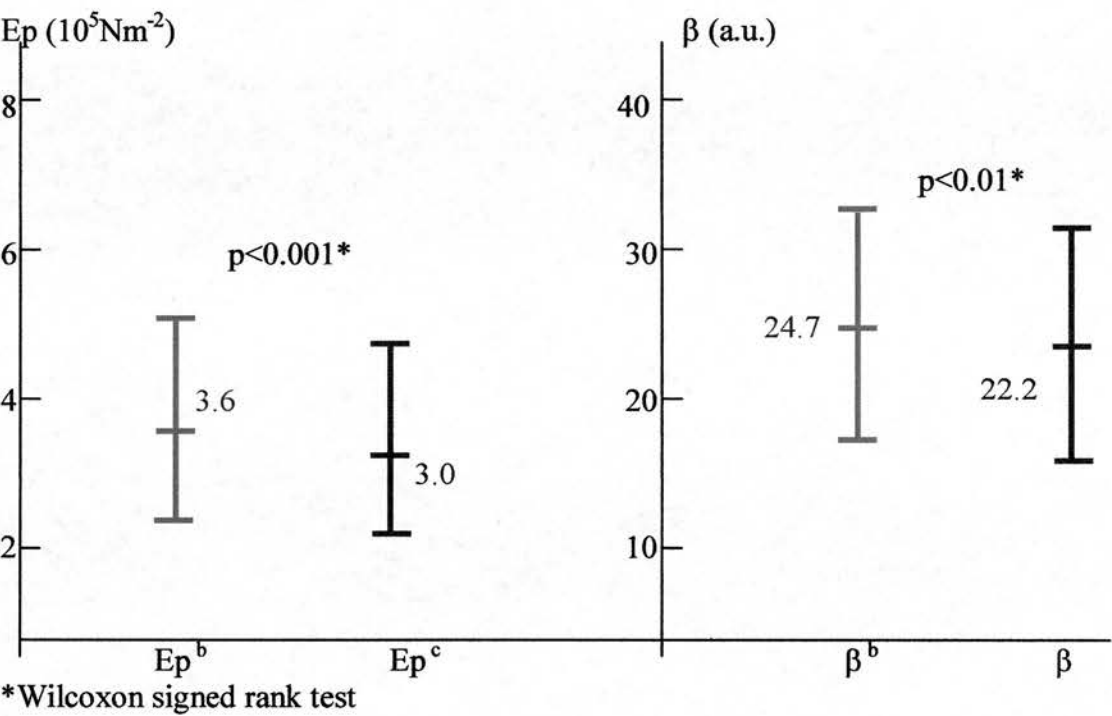
The mean (range) age of the subjects was 74 (63-84) years and the median [interquartile range (IQR)] AP diameter was 44 (40-51) mm. The median (IQR) brachial pressures were systolic 144 (130-164) mmHg, diastolic 76 (71-86) mmHg. The median (IQR) central pressures were systolic 140 (121-153) mmHg, diastolic 76 (72-86) mmHg. The amplification ratio (peripheral PP: central PP) was 1.1.

Derived central systolic pressure, pulse pressure and MAP were significantly lower than the brachial equivalents (Table 6.1). There was no difference with regard to diastolic pressure. The Wilcoxon signed rank test showed that median Ep and β were significantly lower ($p \leq 0.01$) when using central pressure rather than brachial pressure (Table 6.1 and Figure 6.1).

Table 6.1. Comparison of brachial and central pressures and pressure-strain elastic modulus (Ep) and stiffness (β) derived from brachial and central pressures.

Variable	(units)	Brachial Median (IQR)	Central Median (IQR)	Median (IQR) % difference	Wilcoxon signed rank test p (two tailed)
DBP	(mmHg)	76 (71-86)	76 (72-85)	-1 (-3 – 1)	0.5
SBP	(mmHg)	144 (130-164)	140 (121-153)	6 (3-10)	0.001
PP	(mmHg)	65 (50-79)	60 (44-75)	14 (10-23)	0.001
MAP	(mmHg)	100 (89-110)	99 (89-106)	2 (1-6)	0.003
Ep	(10 ⁵ Nm ⁻²)	3.6 (2.4-5.1)	3.0 (2.2-4.9)	13 (5-23)	0.001
β	(a.u.)	24.7 (17.4-33.0)	22.2 (15.5-33.2)	12 (-1 – 20)	0.010

Figure 6.1. Median and IQR values of E_p and β derived from brachial and central pressures.



Bland and Altman plots comparing the agreement between the two methods are shown in Figures (6.2-5).

Figure 6.2. Bland-Altman plot for repeated measures of diastolic pressure using brachial sphygmomanometry and radial applanation tonometry.

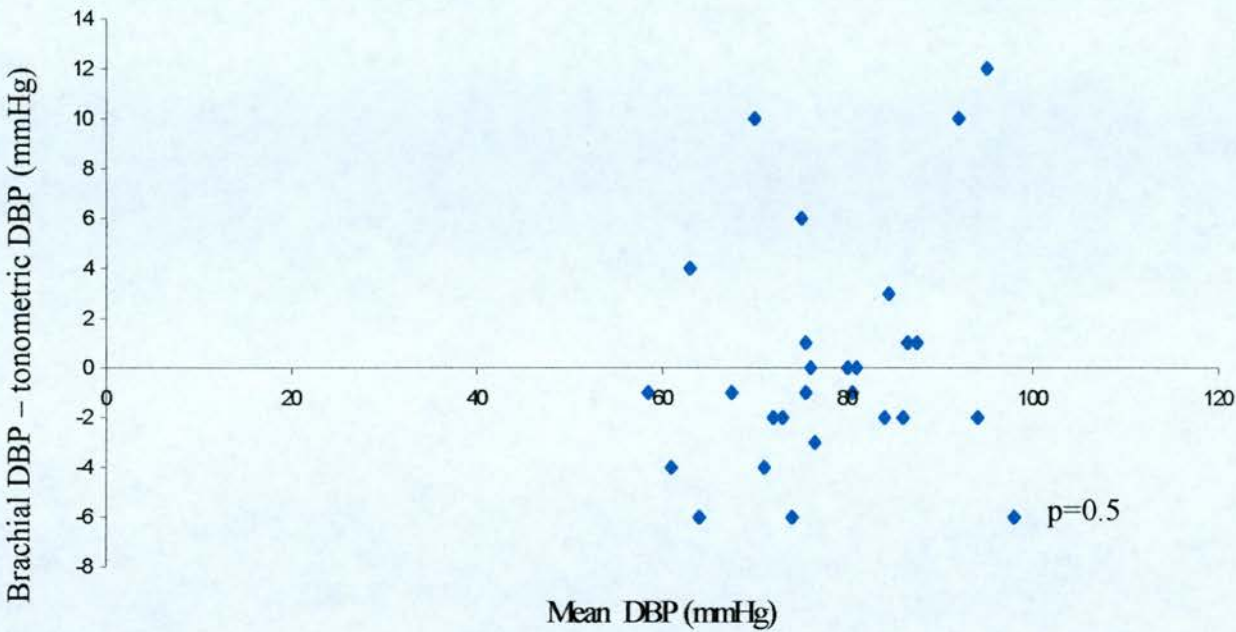


Figure 6.3. Bland-Altman plot for repeated measures of systolic pressure using brachial sphygmomanometry and radial applanation tonometry.

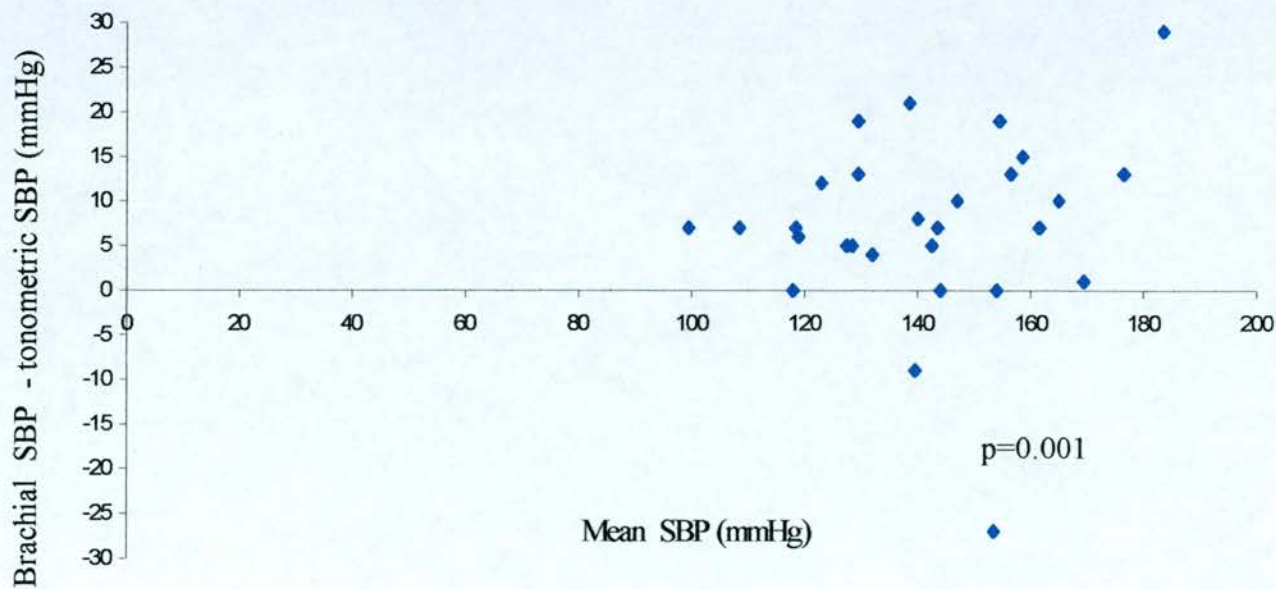


Figure 6.4. Bland-Altman plot for repeated measures of pressure-strain elastic modulus using brachial sphygmomanometry and radial applanation tonometry.

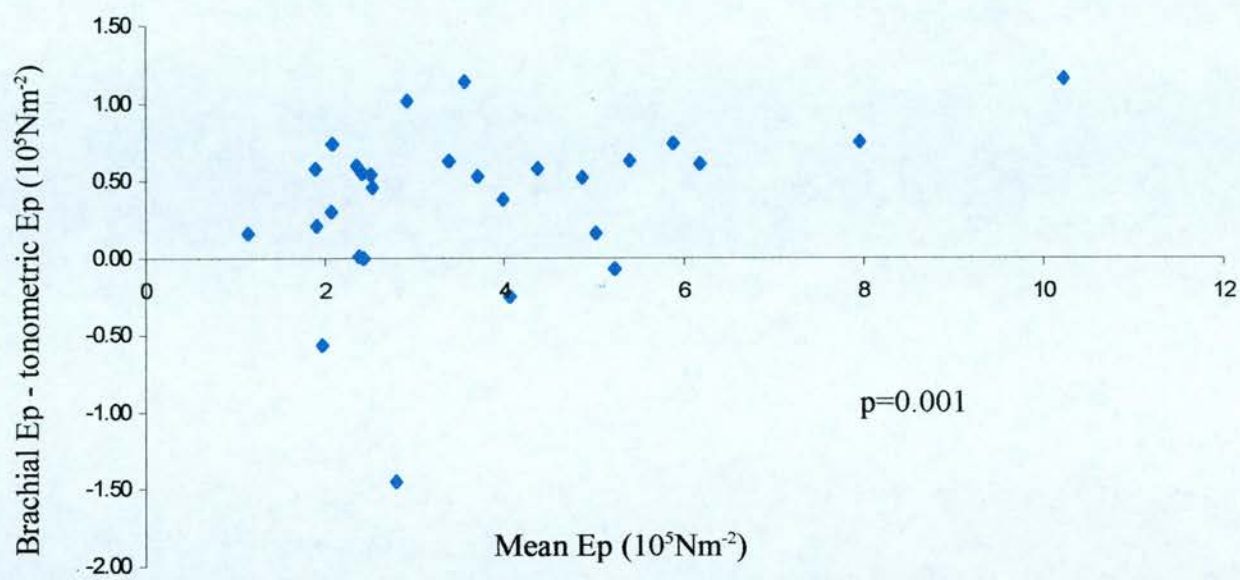
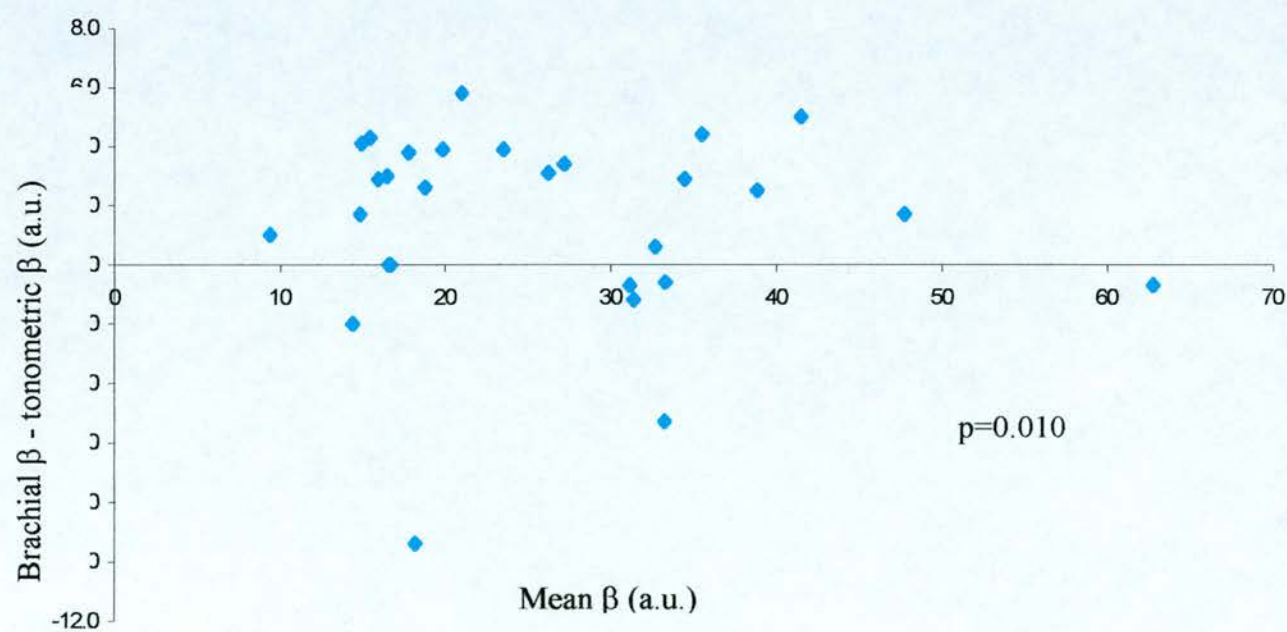


Figure 6.5. Bland-Altman plot for repeated measures of stiffness using brachial sphygmomanometry and radial applanation tonometry.



In order to examine whether the difference in distensibility derived from central and brachial pressures was confounded by age or AAA diameter, predicted log values for central and brachial-derived distensibility adjusted for age and diameter were calculated and compared. The differences between distensibility calculated using brachial and derived central pressures remained significant (Wilcoxon signed rank test, both $p \leq 0.001$). Median (IQR) Ep^b predicted from brachial pressure was 1.22 (1.08-1.45) $10^5 Nm^{-2}$, and Ep^c predicted from central pressure was 1.11 (0.94-1.35) $10^5 Nm^{-2}$. Similarly, β^b predicted from brachial pressure was 3.18 (3.05-3.37), and β^c predicted from central pressure was 3.07 (2.94-3.32).

6.5 Summary

Use of brachial pressure as opposed to central aortic pressure significantly and systematically overestimated Ep by 13% and β by 12% (based on the assumption that Sphygmocor PWA accurately calculates central pressure). The systematic nature of this error suggests that this overestimate is independent of the magnitude of blood pressure.

6.6 Discussion

This study compares the use of non-invasive brachial artery pressure and non-invasive, derived aortic pressure in the measurement of AAA distensibility. Previous work comparing invasive intra-aortic pressure and non-invasive brachial pressure in the assessment of aortic distensibility suggested that using peripheral blood pressure to calculate distensibility underestimates Ep and β by 25-30% (Imura et al 1986, Sonesson *et al* 1994). These studies were performed on young volunteers with normal aortas. The situation with regard to older patients with AAA might be expected to be

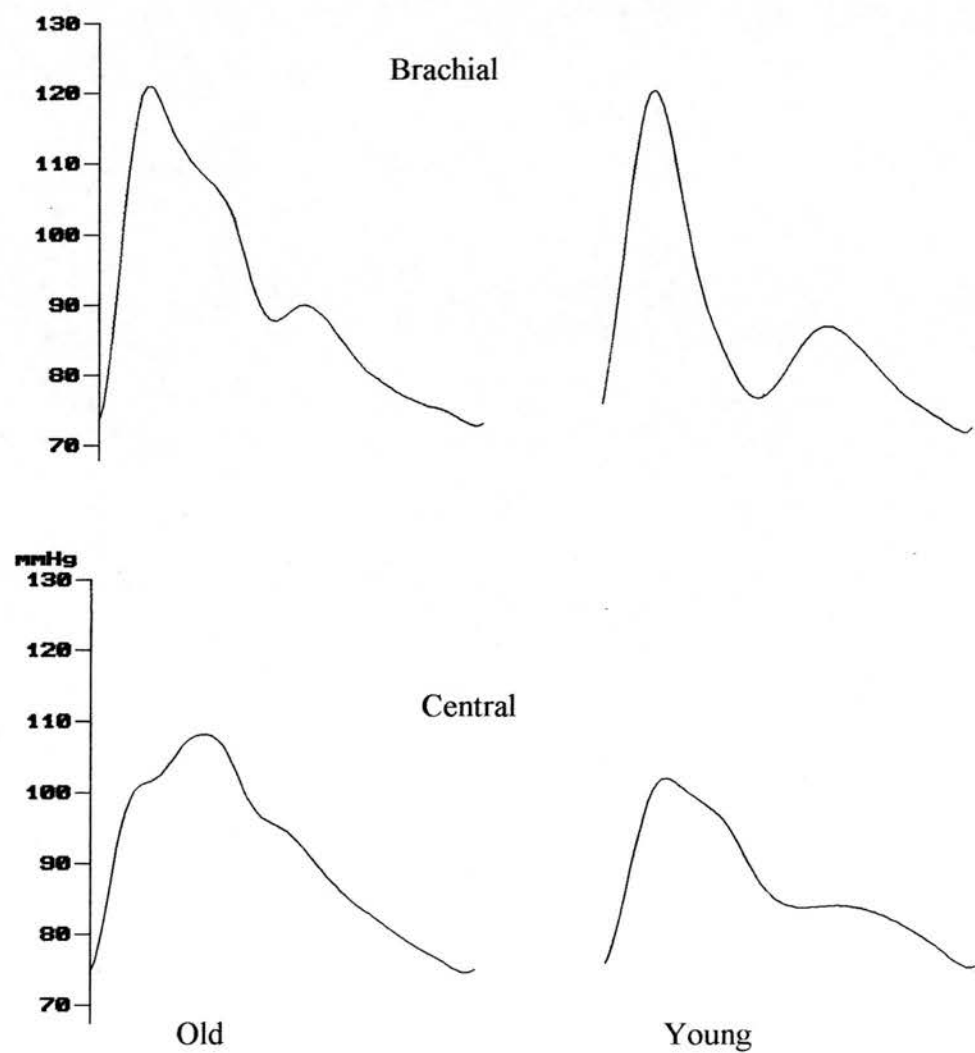
different because of reduced pressure amplification between the aorta and the brachial artery in the elderly.

Imura *et al* (1986), who compared invasive intra-aortic and non-invasive brachial artery pressures, found that brachial systolic and diastolic pressures were higher, and that brachial pulse pressure was lower, than in the aorta. Sonnesson *et al* (1994) also compared invasive arterial pressure at the point of diameter measurement with brachial sphygmomanometry pressure. However, these authors found brachial systolic pressure to be the same or lower than in the aorta, brachial diastolic pressure higher, and consequently brachial pulse pressure lower than in the aorta. Not only are these findings difficult to explain physiologically, but they are also in contrast to the majority of other data as described above and below (Kroeker and Wood 1955, Rowell *et al* 1968, Pauca *et al* 1992). The most likely explanation may be that, because the authors compared invasive aortic pressure measurement with sphygmomanometrically determined brachial artery pressure, the error was dependent on the method, rather than the site, of measurement. Indeed, the inaccuracy of sphygmomanometric blood pressure measurements has been previously reported (Watson *et al* 1998).

As the pressure wave travels through the arterial tree from the large, elastic arteries to the smaller, muscular vessels, the speed and amplitude of the wave increases because of decreasing vessel distensibility. The pressure contour also becomes distorted: the systolic portion is narrowed and elevated; the incisura is damped and eventually disappears; a hump appears in its place in the diastolic portion. This damping of the high frequency components of the pressure wave is attributed to the viscoelastic

properties of the arterial wall. Reflection, vascular tapering and transmission velocity enhance the peaking of the pressure wave. The result is that in the young there is a pronounced difference in central and peripheral pressures, with systolic pressure increasing distally whilst diastolic pressure remains essentially unchanged (Berne and Levy 1998) (Figure 6.6).

Figure 6.6. Central arterial waveform (lower panel) and peripheral waveform (upper panel) in a young (right) and an elderly (left) subject. Reproduced from Wilkinson *et al* (1998b).



Ageing of the arterial tree reduces vessel distensibility (increases stiffness) and markedly reduces the difference between central and peripheral systolic pressure while increasing pulse pressure, especially in the aorta. This is because stiffer arteries transmit the pressure wave at a higher velocity i.e. pulse wave velocity is increased. The result is that a larger than normal reflected pressure wave returns to the heart earlier, augmenting late systolic peak pressure (Kroeker and Wood 1955). Thus, while age increases aortic systolic pressure, peripheral systolic pressure is much less affected, so the gradient between central and peripheral systolic pressure is reduced Pauca *et al* (1992). Pauca *et al* (1992) examined a group of subjects aged 48-77 (median 61) years and found the difference between radial systolic pressure and ascending aortic systolic pressure to be an increase of 12 mmHg, diastolic decreased by 1 mmHg. In the present study, the median brachial-central pressure difference was 7 mmHg for systolic pressure and there was no significant difference in diastolic pressure. The lower difference in systolic pressure and the amplification ratio (peripheral pulse pressure: central pulse pressure) of 1.1 reflects the older age of our study population (68-84, median 74 years).

Abdominal aortic pressure remains difficult to measure non-invasively at present. The PWA derived ascending aortic pressure is the closest approximation available and may be considerably closer than brachial artery pressure. However, validation of Sphygmocor is currently being debated. Validation of the use of a GTF has been carried out by previous workers using similar, but not the same, technology (Karamanoglu *et al* 1993, Chen *et al* 1996, Chen *et al* 1997, Fetics *et al* 1999). Karamanoglu *et al* (1993) and Fetics *et al* (1999) used the same GTF as that used by Sphygmocor, while Chen *et al* (1996) and (1997) used a different GTF. These studies

compared invasive ascending aortic pressures with radial tonometric pressures and showed that when a GTF was applied to radial pressures the reconstructed central pressure waveform was clinically accurate for systolic and pulse pressures. Although work carried out by the developers and published as an abstract suggested that ‘...ascending aortic augmentation [could] be determined to a reasonable approximation from the radial artery pulse using a generalised transfer function’ (O’Rourke *et al* 1995), validation of the Sphygmocor system has not yet been independently carried out and published. O’Rourke *et al* (1995) did not publish a clear description of the method used.

In spite of this, several independent studies have now been carried out assessing the reproducibility of the Sphygmocor device and using it (and its GTF) as a ‘validated’ blood pressure measurement tool (Wilkinson *et al* 1998a, Seibenhofer *et al* 1999, Brown 1999, Covic *et al* 2000, Segers *et al* 2000, Segers *et al* 2001). The general consensus would appear to be that although individualised transfer functions may provide more accurate derived central pressure wave contours, a GTF is adequate. In response to these publications, one author has raised concerns regarding the paucity of published evidence of the validity of the Sphygmocor device and the GTF it uses to derive aortic arch pressure from radial pressure (Lehmann ED 2000, Lehmann ED 2001a, Lehmann ED 2001b, Lehmann ED 2001c).

It is beyond the scope of this thesis to investigate the validity of the Sphygmocor PWA device but the concerns raised by Lehmann (2000, 2001a,b,c) should be acknowledged. The aim of this chapter was to investigate the error caused by use of non-invasive brachial pressure instead of invasive intra-AAA pressure in the

calculation of E_p and β . Invasive intra-AAA pressure measurement was, however, not an option and the only non-invasive method of aortic pressure measurement available to this author at the time of study was the Sphygmocor PWA device.

The principal finding of the study, based on the assumption that Sphygmocor PWA accurately calculates central pressure, was that use of brachial pressure as opposed to central aortic pressure may have significantly increased E_p by 13% and β by 12%.

The error was a systematic overestimate of E_p and β and as such will not affect comparisons between subjects or over time. The systematic nature of these findings suggests that this overestimate is independent of the magnitude of blood pressure and therefore applies to all subjects of comparable ages regardless of the presence of hyper- or hypotension. The importance of these findings is that this non-invasive method of aortic wall distensibility measurement (Diamove) can be used successfully in the clinical setting in conjunction with brachial sphygmomanometry.

Previous findings of this group (Wilson *et al* 1998, Wilson *et al* 2001) suggest that routine follow-up of distensibility and diameter could provide a greater understanding of AAA wall degeneration than diameter alone. If this is the case then the systematic nature of the error should not bias the measurements because it is likely to be the change in the measurements over time that provides the important information and not the absolute values. However, a study comparing distensibility calculated using invasive aortic pressure at the site of the AAA with that using derived central pressures and with non-invasive brachial pressures may provide more accurate data.

6.7 Conclusions

The overestimate of E_p and β is viewed to be small and therefore acceptable clinically. The linearity of the relationship between central and peripherally derived distensibility shows that the error is a systematic overestimate. However, since the discrepancy between central and peripheral systolic pressure (i.e. pressure amplification) is age-dependent, greater differences between E_p^b/β^b and E_p^c/β^c may occur in younger individuals, and care must be exercised when comparing measures of distensibility based on peripheral blood pressure measurements between age groups. The validity of the Sphygmocor may require more rigorous study.

Chapter 7. Follow-up and endpoints of interest of the study population

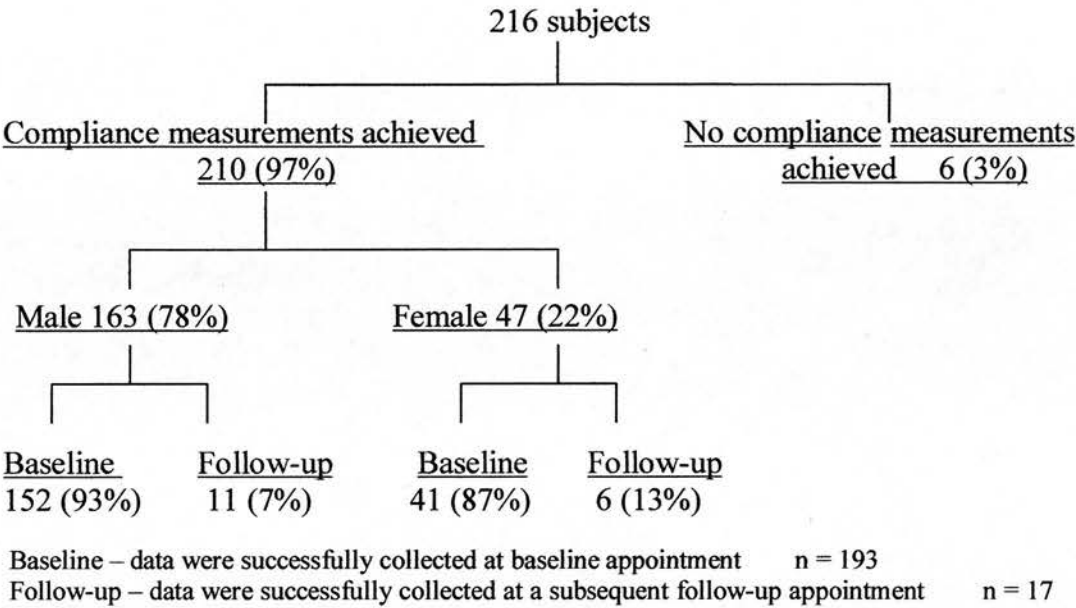
7.1 Introduction

This chapter describes patient follow-up and the outcome events leading to the cessation of follow-up. Further details of the numbers of patients in each part of the analysis are given in Appendix III.

7.2 Study population

The collection of compliance data is shown in Figure 7.1. Data could not be collected on 6 patients; three due to obesity and shortness of breath, and three due to cardiac arrhythmia (see Chapter 4). The first data set was collected at baseline in 193 patients; in another 17 patients, the first data set set was collected at a later visit, thus the total number of patients with usable data collected at baseline or at any subsequent visit was 210 (Appendix III).

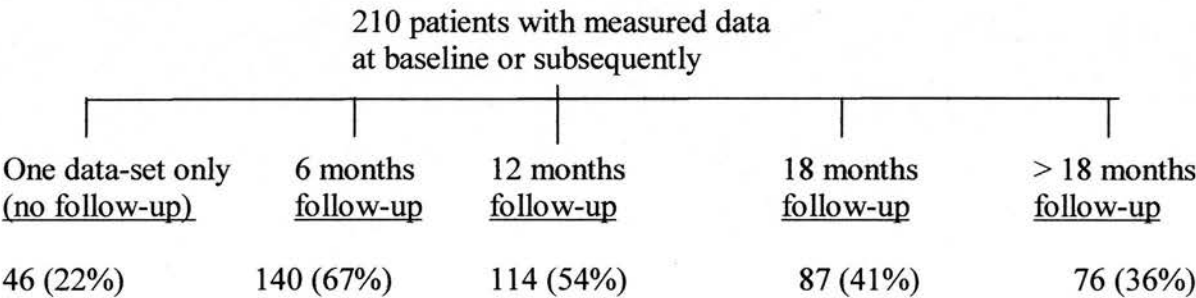
Figure 7.1. Data collection in the study population as a whole.



7.3 Length of follow-up

For logistical reasons, as the number of patients in the study grew, the follow-up interval was reduced from three to six months. At the end of the study, 164 (76%) of the study population had at least two compliance data sets, 102 (47%) at least four, and 71 (33%) had at least five (Figure 7.3).

Figure 7.3: Length of follow-up of patients on whom usable waves were achieved at any time.



Percentages given are the cumulative % of patients followed for at least that length of time.

7.4 Outcome events

7.4.1 Outcome measures

Follow-up was discontinued when the AAA ruptured or was repaired, when the patient died, could no longer produce compliance data, or no longer wished to attend. Cause of death was collected by means of hospital records and Central Registry notification.

Death ended follow-up for 49 patients during the study. 28 patients suffered ruptured AAA, of whom 24 died (Table 7.1, Figures 7.4 and 5). During the study, AAA in 17 (10%) male patients ruptured compared with 11 (23%) in the female patients (Figure 7.6). Although there were more females than males in the rupture group (χ^2 $p \leq 0.04$) there were more males than females in the asymptomatic elective group (χ^2 $p \leq 0.03$). The proportions of males and females in the intact AAA and symptomatic groups were not significantly different (Figures 7.7 and 7.8). It should be noted that the AAA that had not been operated on and had not ruptured by the end of the study have been described throughout as 'intact AAA'.

Figure 7.4: Flow chart of age, sex and outcome measures in 210 subjects who produced usable data at baseline or at a subsequent follow-up visit.

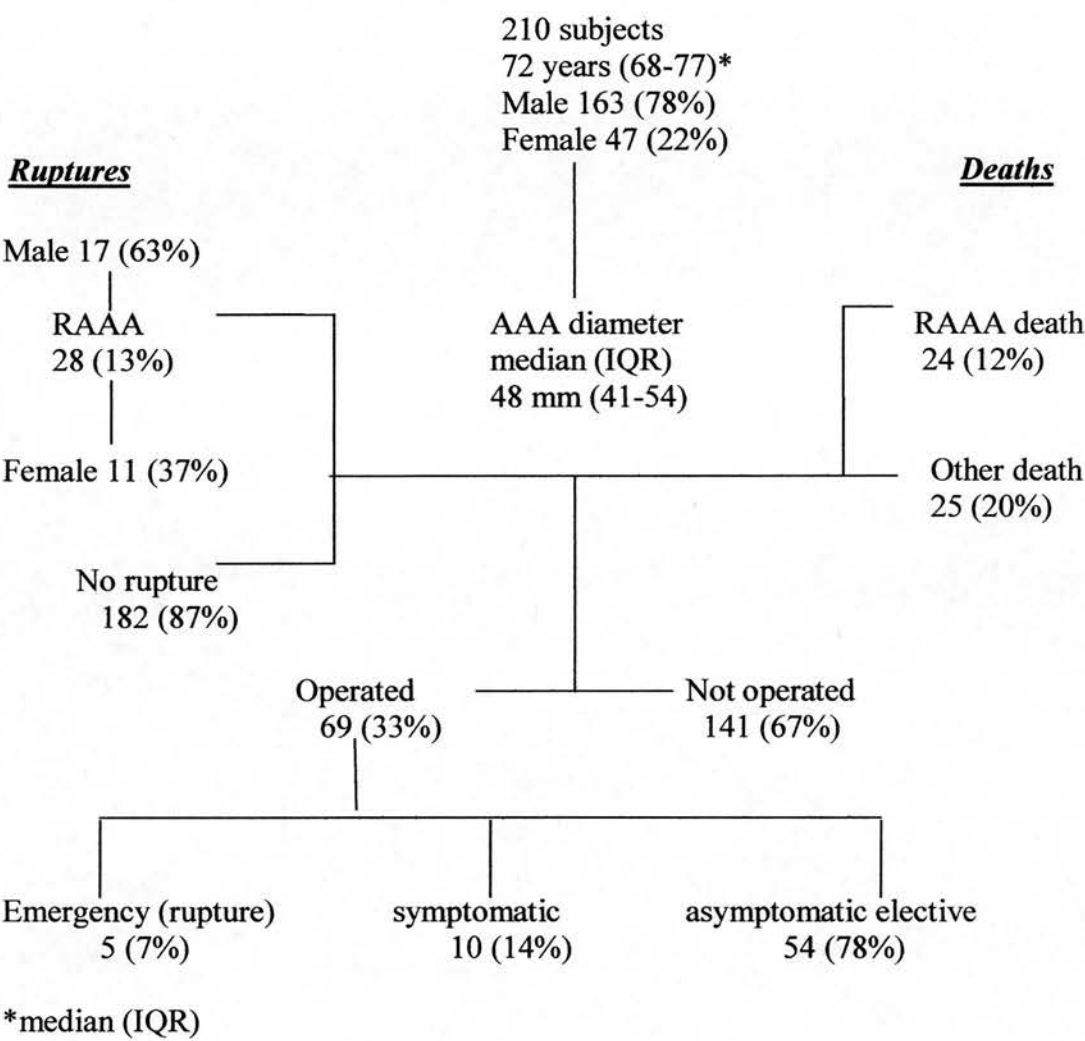


Table 7.1: Numbers of patients for whom follow-up was discontinued and the reasons.

Reason	Total	F-up 1	F-up 2	F-up 3	F-up 4	F-up 5+
Deceased	49	9	9	13	7	11
Surgery	66	20	11	11	10	14
Refusal	5	1	1	2	0	1
No waves	3	0	0	2	0	1
Unfit	12	0	5	1	3	3
End of study	74	0	1	5	16	52
Unknown	1	0	0	0	0	1

Figure 7.5: Pie chart of the reasons for the end of follow-up.

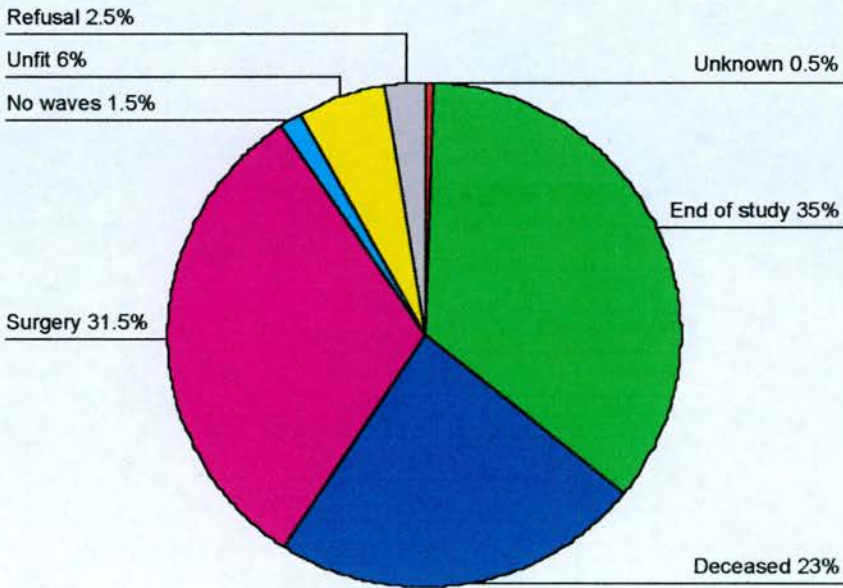
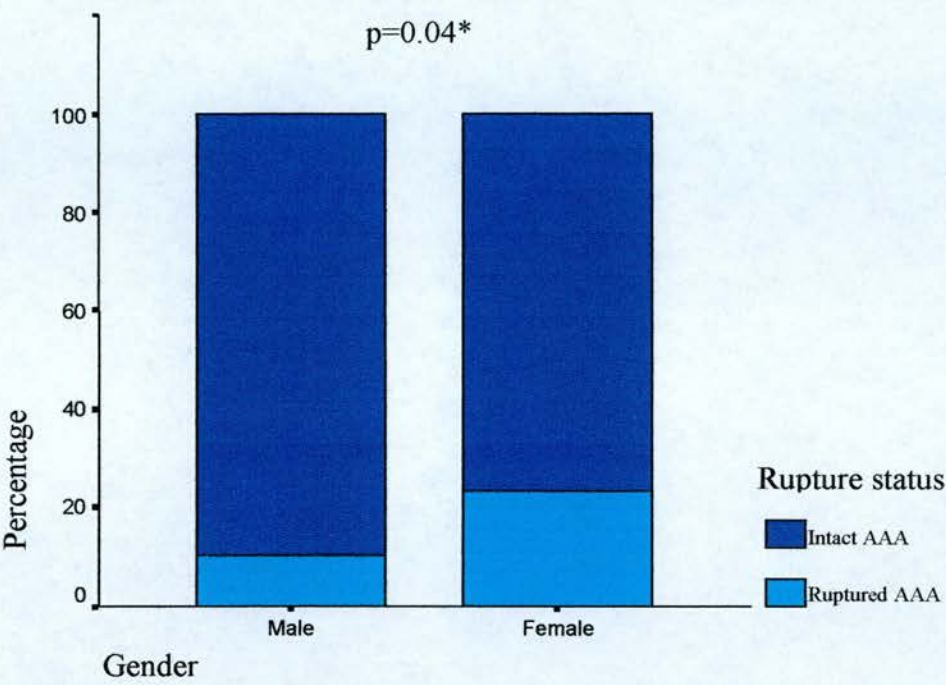


Figure 7.6. Comparison of the proportion of AAA rupturing within males and females.



* χ^2 test

Figure 7.7. Surgical outcome in 73 males whose AAA underwent rupture or repair.

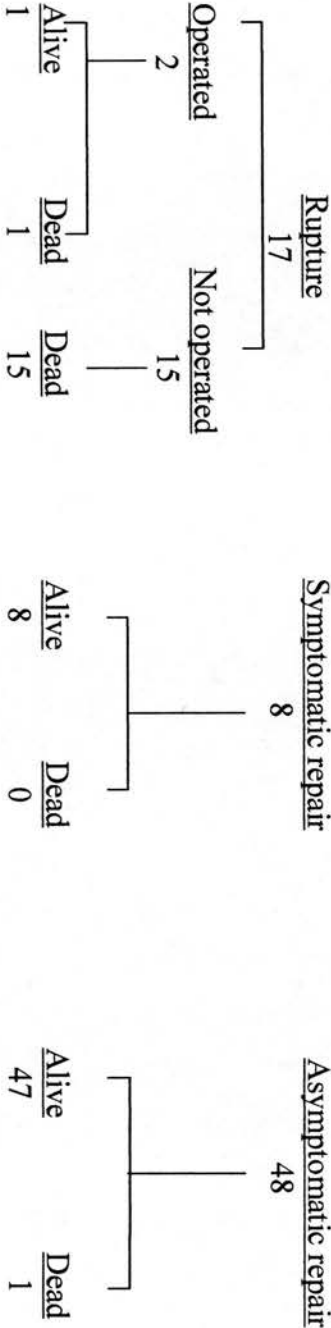
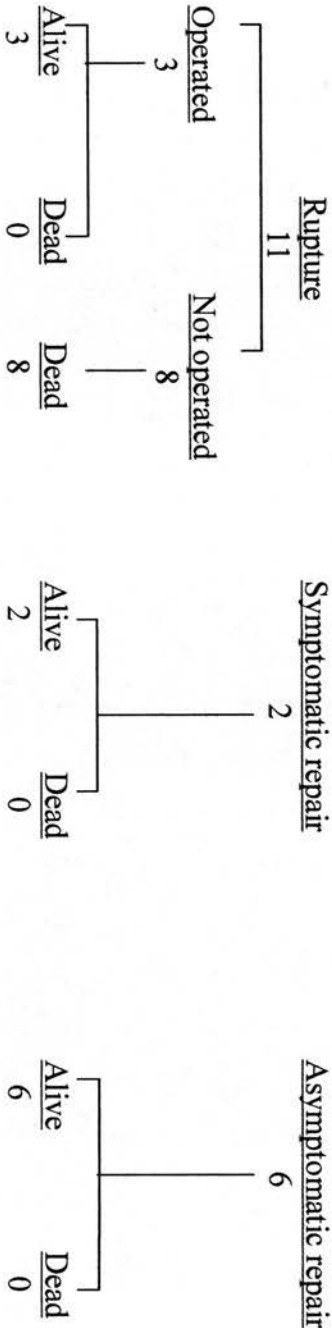


Figure 7.8. Surgical outcome in 19 females whose AAA underwent rupture or repair.



7.5 Summary

- 216 subjects were recruited, of which 210 produced usable data.
- 193 (89%) produced usable data at baseline and a further 17 (8%) produced usable data at subsequent follow-up appointments.
- Failure to produce usable data was due to obesity, cardio-respiratory disease and arrhythmia; it was unrelated to gender.
- Of those who produced usable data, 54% were followed for 12 months and 36% of subjects were followed for more than 18 months.
- 63% of AAA ruptures occurred in males.
- AAA rupture occurred in a significantly higher proportion of females than males (23% and 10% respectively).

7.6 Conclusions

In approximately 3% of subjects, distensibility measurement may not be possible.

Females in this study population were more likely to suffer ruptured AAA.

Chapter 8. Baseline statistics

8.1 Introduction

This chapter describes the baseline demographics and variables. Further details of the numbers of patients in each part of the analysis are given in Appendix III.

8.2. Baseline data

8.2.1 Clinical data

Baseline variables (Table 8.1), with the exception of age, were skewed and so non-parametric statistical methods have been used. Baseline blood pressure was obtained in 194 patients and baseline diameter and distensibility data in 193 (Chapter 7 and Appendix III).

Table 8. 1: Median and interquartile range (IQR) of the variables measured on 193 subjects (152 males: 41 females) who produced usable data at baseline.

Variable		Median (IQR)	Data points
Age	(years)	72 (68-77)	210
DBP	(mmHg)	80 (72-90)	194
SBP	(mmHg)	140 (130-160)	194
PP	(mmHg)	60 (50-75)	194
MAP	(mmHg)	102 (93-111)	194
Dmax	(mm)	47.9 (41.0-53.7)	193
Ep	(10 ⁵ Nm ⁻²)	2.91 (1.99-4.37)	193
β	(a.u.)	19.4 (14.4-29.4)	193

8.2 Univariate analyses of baseline data

8.2.1 Correlations between variables at baseline

The correlations between baseline variables are shown in Table 8.2.

Table 8. 2: Spearman's correlation coefficients describing the relationships between baseline variables in 193 subjects from whom usable data were collected (at baseline).

	Age	DBP (mmHg)	SBP (mmHg)	PP (mmHg)	MAP (mmHg)	Dmax (mm)	Ep (10 ⁵ Nm ⁻²)
DBP (mmHg)	0.08 p≤0.24						
SBP (mmHg)	0.07 p≤0.36	0.52 p≤0.01					
PP (mmHg)	0.04 p≤0.58	0.01 p≤0.90	0.83 p≤0.01				
MAP (mmHg)	0.09 p≤0.22	0.87 p≤0.01	0.85 p≤0.01	0.45 p≤0.01			
Dmax (mm)	0.33 p≤0.01	0.21 p≤0.01	0.06 p≤0.40	-0.07 p≤0.33	0.16 p≤0.03		
Ep (10 ⁵ Nm ⁻²)	-0.08 p≤0.24	0.14 p≤0.06	0.46 p≤0.01	0.46 p≤0.01	0.32 p≤0.01	0.16 p≤0.03	
β (a.u.)	-0.11 p≤0.13	-0.48 p≤0.51	0.28 p≤0.01	0.37 p≤0.01	0.11 p≤0.13	0.14 p≤0.05	0.97 p≤0.01

Bold denotes significant values

8.3 Univariate analysis of baseline data by gender

8.3.1 Comparison of baseline data by gender

There was a trend towards increased AAA distensibility in women (Table 8.3).

Table 8.3. A comparison of median (IQR) measurements in 152 males and 41 females on whom distensibility data were collected at baseline.

		Males (n=152)	Females (n=41)	Mann-Whitney U test, p
Age	(years*)	73 (68-77)	72 (68-77)	0.94
DBP	(mmHg*)	80 (74-90)	80 (60-122)	0.70
SBP	(mmHg*)	140 (102-210)	148 (100-212)	0.67
PP	(mmHg*)	60 (20-130)	64 (18-112)	0.56
MAP	(mmHg*)	103 (93-112)	102 (93-110)	0.89
Dmax	(mm)	49 (42-54)	44 (40-54)	0.20
Ep	(10 ⁵ Nm ⁻²)	3.03 (2.08-4.55)	2.37 (1.91-3.31)	0.07
β	(a.u.)	20.7 (14.8-29.6)	17.0 (12.7-24.6)	0.06

* 42 females had age and blood pressure data.

8.3.2 Relationships between baseline variables analysed by gender

Several baseline variables exhibited gender-dependent correlations (Table 8.4).

Table 8.4. Spearman's correlation coefficients describing the relationships between baseline measured variables by gender.

	Males (152)			Females (41)		
	Diameter	Ep	β	Diameter	Ep	β
Age	0.33 p≤0.001	-0.06 p≤0.46	-0.07 p≤0.42	0.33 p≤0.04	-0.18 p≤0.27	-0.27 p≤0.08
DBP	0.15 p≤0.07	0.19 p≤0.02	0.003 p≤0.97	0.36 p≤0.02	-0.05 p≤0.75	-0.22 p≤0.10
SBP	0.01 p≤0.90	0.46 p≤0.01	0.29 p≤0.01	0.32 p≤0.04	0.44 p≤0.01	0.22 p≤0.17
PP	-0.07 p≤0.40	0.44 p≤0.01	0.34 p≤0.01	-0.07 p≤0.66	0.59 p≤0.01	0.52 p≤0.01
MAP	0.09 p≤0.29	0.36 p≤0.01	0.15 p≤0.06	0.40 p≤0.01	0.15 p≤0.36	-0.10 p≤0.55
Dmax	- p≤0.03	0.18 p≤0.03	0.17 p≤0.04	- p≤0.86	0.03 p≤0.86	-0.06 p≤0.72

Significant values are in bold

8.4 Univariate analysis of baseline data by outcome

8.4.1 Comparison of baseline data by outcome

Some baseline variables and their interrelationships were related to outcome (Table 8.5 and 8.6).

Table 8.5. Medians and (IQR) of baseline variables divided according to outcome status.

	All	RAAA	Symptomatic repair	Asymptomatic repair	Intact AAA	Kruskal- Wallis, p
n	210	28	10	53	119	
Age (years)	73 (68-77)	77 (73-80)	71 (66-78)	71 (66-75)	72.5 (68-77)	0.01
n	194	26	7	53	108	
DBP (mmHg)	80(72-90)	86 (80-90)	78 (70-80)	80 (70-88)	80 (72.5-90)	0.11
SBP (mmHg)	140 (130-160)	141 (120-150)	160 (130-170)	140 (132-152)	140 (128-162)	0.58
PP (mmHg)	60 (50-75)	51 (42-64)	90 (50-92)	60 (50-72)	62 (50-72)	0.03
MAP (mmHg)	102 (93-111)	106 (93-112)	103 (90-109)	101 (93-111)	101 (93-112)	0.85
n	193	26	7	53	107	
Dmax (mm)	48 (41-54)	53 (47-64)	49 (48-53)	50 (48-55)	43(38-50)	0.01
Ep (10 ⁵ Nm ⁻²)	2.9 (2.0-4.4)	2.6 (2.0-3.5)	2.78 (1.68-4.43)	2.94 (2.17-4.52)	2.91 (1.92-4.48)	0.60
β (a.u.)	19.4 (14.4-29.4)	16.5 (13.5-23.2)	19.8 (13.4-28.1)	20.8 (15.3-29.5)	19.5 (14.2-29.6)	0.40

Table 8.6. Correlation coefficients between baseline measured variables within outcome groups.

<u>Intact AAA (N=107)</u>				<u>Ruptured AAA (N=26)</u>			
	Dmax (mm)	Ep (10 ⁵ Nm ⁻²)	β (a.u.)		Dmax (mm)	Ep (10 ⁵ Nm ⁻²)	β (a.u.)
Age (years)	0.35 p≤0.01	-0.18 p≤0.07	-0.20 p≤0.03		0.38 p≤0.06	0.22 p≤0.28	0.32 p≤0.12
DBP (mmHg)	0.16 p≤0.09	0.12 p≤0.23	-0.07 p≤0.45		0.17 p≤0.40	0.08 p≤0.71	-0.15 p≤0.45
SBP (mmHg)	0.05 p≤0.62	0.50 p≤0.01	0.31 p≤0.01		0.12 p≤0.56	0.16 p≤0.45	-0.06 p≤0.78
PP (mmHg)	-0.06 p≤0.52	0.53 p≤0.01	0.42 p≤0.01		0.14 p≤0.50	0.18 p≤0.37	0.06 p≤0.76
MAP (mmHg)	0.13 p≤0.17	0.32 p≤0.01	0.11 p≤0.26		0.18 p≤0.38	0.13 p≤0.53	-0.11 p≤0.58
Dmax (mm)	-	0.15 p≤0.13	0.14 p≤0.15		-	0.41 p≤0.04	0.36 p≤0.07

8.5 Summary

- AAA diameter was significantly related to age, diastolic pressure, MAP and distensibility at baseline in the group as a whole.
- There were no significant gender-dependent differences in any of the variables although distensibility tended toward being higher in females.
- The relationships between the variables were different between the genders.
- Age and diameter were both greater in the rupture group compared with the intact AAA group.

8.6 Discussion

At baseline, there was a significant inverse relationship between distensibility and diameter, and diameter increased with age. Although AAA diameters were similar in males and females, AAA in females were more likely to rupture. AAA that ruptured were larger, and found in older patients, at baseline. Larger AAA tended to be less distensible. The relationships between distensibility and blood pressure were different in the rupture and intact groups. The median (IQR) time between baseline data and the outcomes of interest was 20 (9-30) months. In order to examine the relationships between these variable closer to the time of rupture, the data collected closer to the time of rupture have been analysed in the following chapter.

8.8 Conclusions

AAA in females ruptured more frequently than in males of the same age, blood pressure and AAA diameter. The AAA that ruptured, or were more likely to rupture (female AAA), exhibited different dynamic relations between diameter and distensibility compared with AAA that remained intact. Baseline data may not

accurately represent AAA dynamics at the time of rupture because of the time elapsed between baseline and outcome.

Chapter 9. Descriptive statistics for last follow-up data

9.1 Introduction

210 patients produced usable data prior to an outcome of interest (see Appendix III). The median (IQR) time difference between baseline data and the outcome of interest was 20 (9-30) months. Baseline data may not reflect wall structure and distensibility immediately prior to AAA rupture, so data measured at the last follow-up prior to the outcome event have been analysed in the same way.

9.2 Data collected at last follow-up

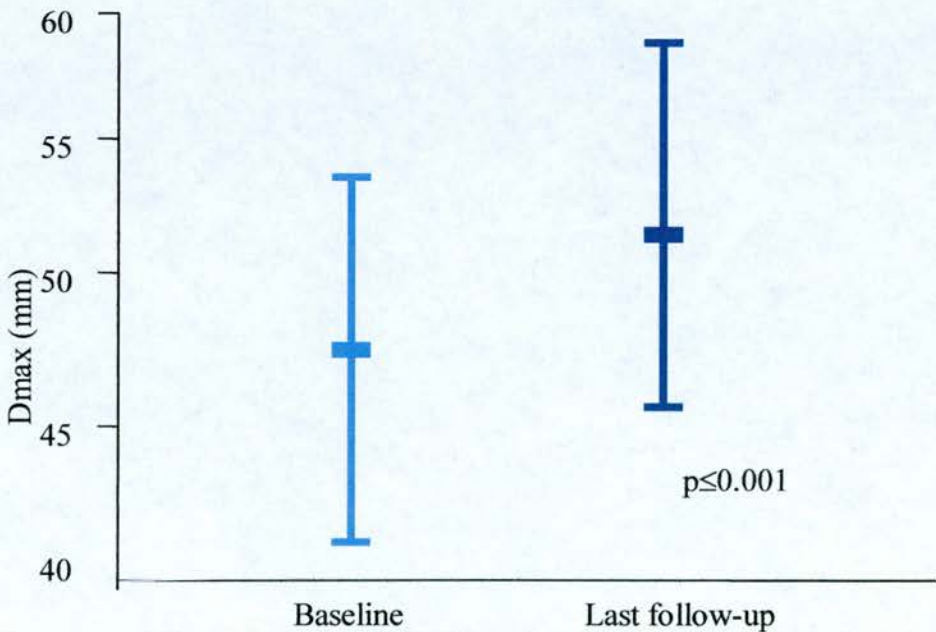
9.2.1 Descriptive statistics of last follow-up data

The median (IQR) time difference between last data collection and outcome for the rupture group was 102 (62-268) days [3.5 (2-9) months], for the asymptomatic AAA repair group it was 51 (13-90) days or 2 (0.4-3) months, and for the symptomatic repair group it was 116 (78-265) days or 3.9 (2.6-8.8) months. In patients undergoing elective repair the arranged admission allowed final measurement a few days before the operation in many cases. The Wilcoxon signed rank test was used to compare baseline and last follow-up data (BP, Dmax, Ep, β) on the 154 subjects who had both data sets. Compared to the baseline data, SBP, PP and MAP were not significantly different ($p=0.53$, $p=0.47$, $p=0.11$ respectively). However, DBP ($p=0.04$), Dmax, Ep and β had each increased significantly (Figures 9.1-3).

Table 9. 1. Blood pressure, diameter and distensibility of the study population at last follow-up.

Variable		Median (IQR)	
n		210	
DBP	(mmHg)	82	(74-90)
SBP	(mmHg)	145	(130-161)
PP	(mmHg)	61	(48-77)
MAP	(mmHg)	103	(94-113)
Dmax	(mm)	51.5	(45-59)
Ep	(10 ⁵ Nm ⁻²)	3.4	(2.3-4.7)
β	(a.u.)	22.2	(15.9-30.6)

Figure 9.1 Comparison of median (IQR) of diameter at baseline and last follow-up in 154 subjects who had both data sets.



Bars represent the median and the IQR of diameter. Wilcoxon signed rank test on paired data sets.

Figure 9.2. Comparison of median (IQR) of E_p at baseline and last follow-up on 154 subjects who had both data sets.

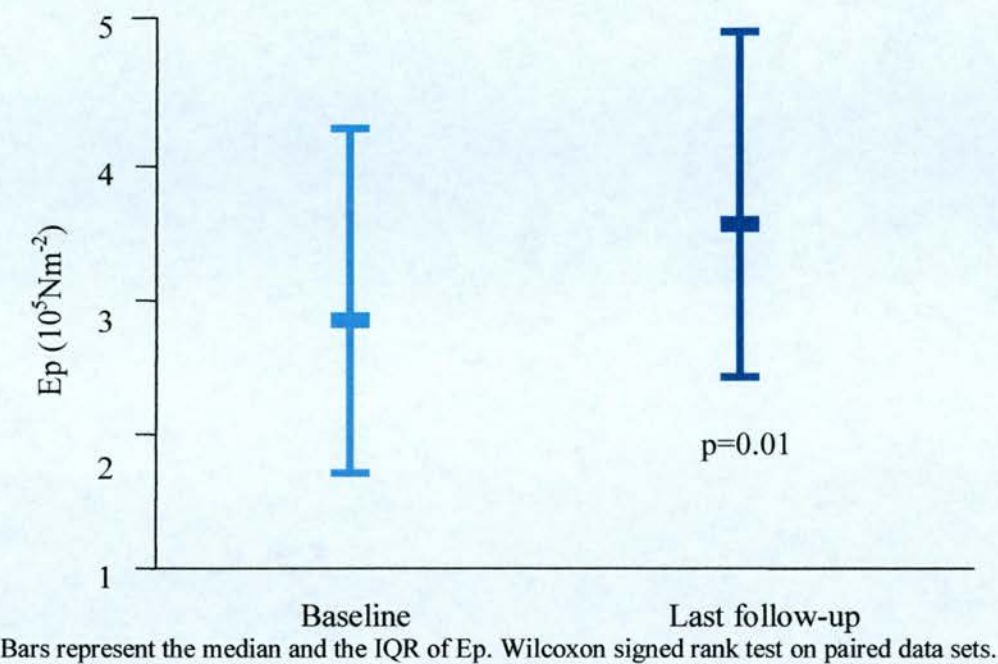
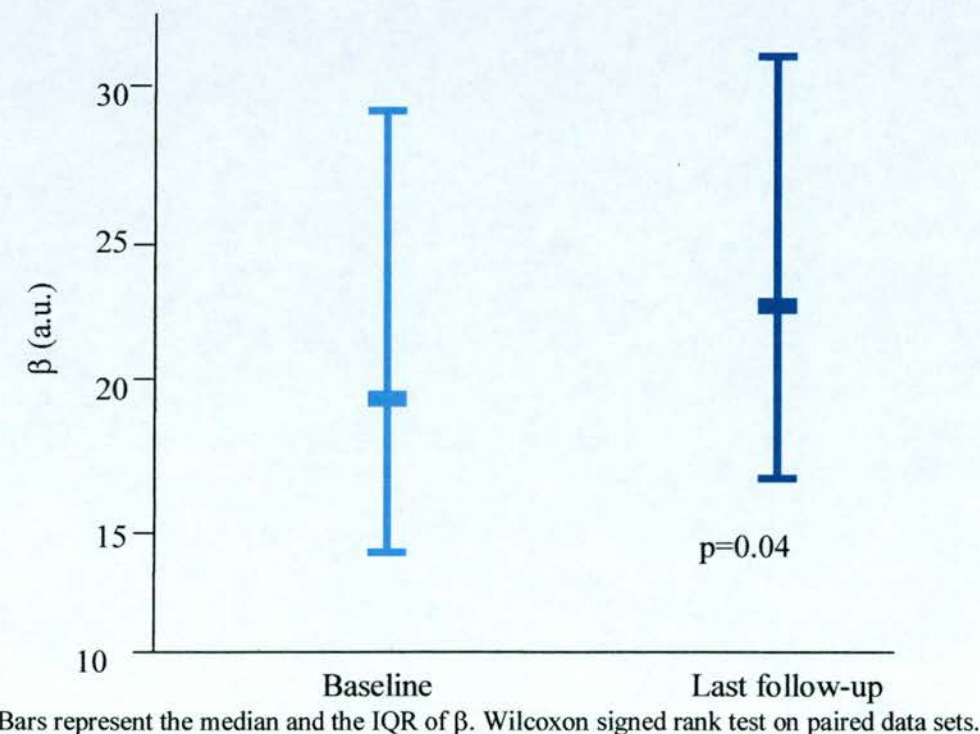


Figure 9.3. Comparison of median (IQR) of β at baseline and last follow-up on 154 subjects who had both data sets.



9.2.2 Correlations between variables at last follow-up

At last follow-up E_p and β were not related to maximum diameter in the group as a whole. This is in contrast to the significant correlations found between these variables at baseline (Table 9. 2).

Table 9. 2: Spearman's correlation coefficients describing the relationship between last follow-up variables in 210 subjects.

	DBP (mmHg)	SBP (mmHg)	PP (mmHg)	MAP (mmHg)	Dmax (mm)	Ep (10 ⁵ Nm ⁻²)
SBP (mmHg)	0.52 p≤0.01					
PP (mmHg)	-0.01 p≤0.87	0.82 p≤0.01				
MAP (mmHg)	0.88 p≤0.01	0.86 p≤0.01	0.43 p≤0.01			
Dmax (mm)	0.16 p≤0.02	-0.10 p≤0.14	-0.22 p≤0.01	0.04 p≤0.60		
Ep (10 ⁵ Nm ⁻²)	0.10 p≤0.15	0.41 p≤0.01	0.42 p≤0.01	0.29 p≤0.01	0.06 p≤0.41	
β (a.u.)	-0.09 p≤0.18	0.22 p≤0.01	0.32 p≤0.01	0.07 p≤0.31	0.06 p≤0.41	0.96 p≤0.01

Bold denotes significant correlation coefficients

9.3 Last follow-up data analysed by gender

9.3.1 Differences in last follow-up data by gender

There were no statistically significant differences between male and female subjects with regard to any of the variables at last follow-up. However, there was a trend toward female patients having more distensible AAA.

9.3.2 Relationships between the variables within each gender

In male patients at last follow-up, maximal AAA diameter was no longer significantly correlated with Ep or β . There remained no significant relationship between diameter and Ep or β at last follow-up in females.

9.4 Last follow-up data by outcome

9.4.1 Last follow-up data by outcome

At last follow-up, median age was higher in the rupture group (78 years vs 75 years). There were significant differences in diastolic pressure and diameter (Figures 9.4 to 9.7), but not in Ep or β , between the outcome categories.

9.4.2 Last follow-up data by outcome and gender

In males, diastolic pressure and maximum diameter remained significantly higher in the rupture group (Table 9.4 and Figure 9.8). In females, diameter was the only variable that was significantly different between the outcome groups; the rupture group had larger AAA diameter than the intact AAA group (Table 9.4 and Figure 9.8). Ep and β were not significantly different between the outcome groups for

either males or females. This is reflected in the 10-fold difference in the median of both variables (Table 9.4).

Figure 9.4. Differences in median (IQR and range) diastolic blood pressure between outcome groups at last follow-up.

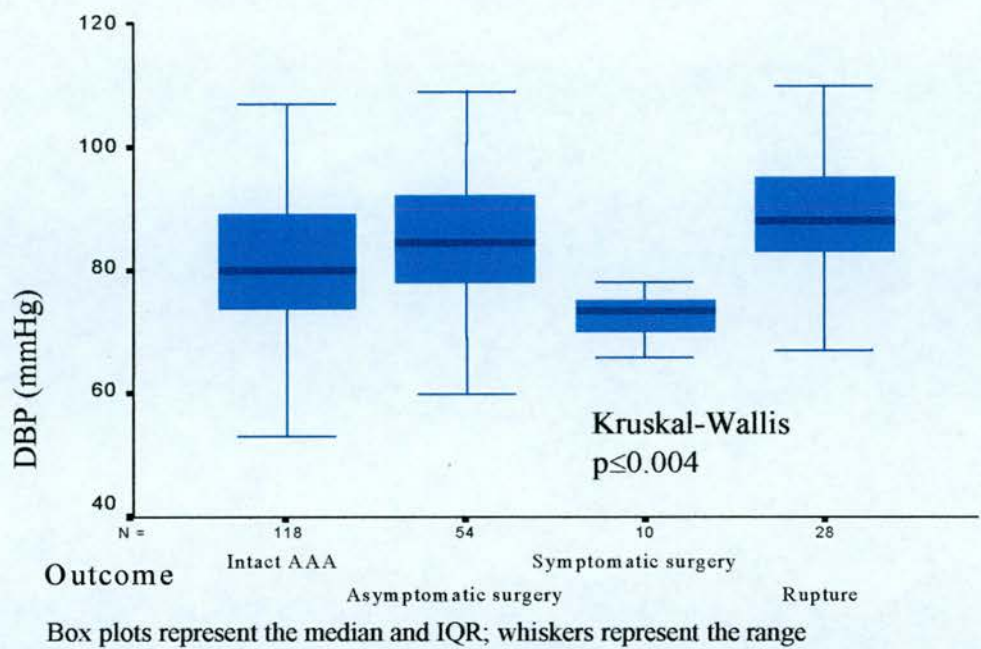


Figure 9.5. Differences in last follow-up diastolic blood pressure between intact AAA and ruptured AAA categories.

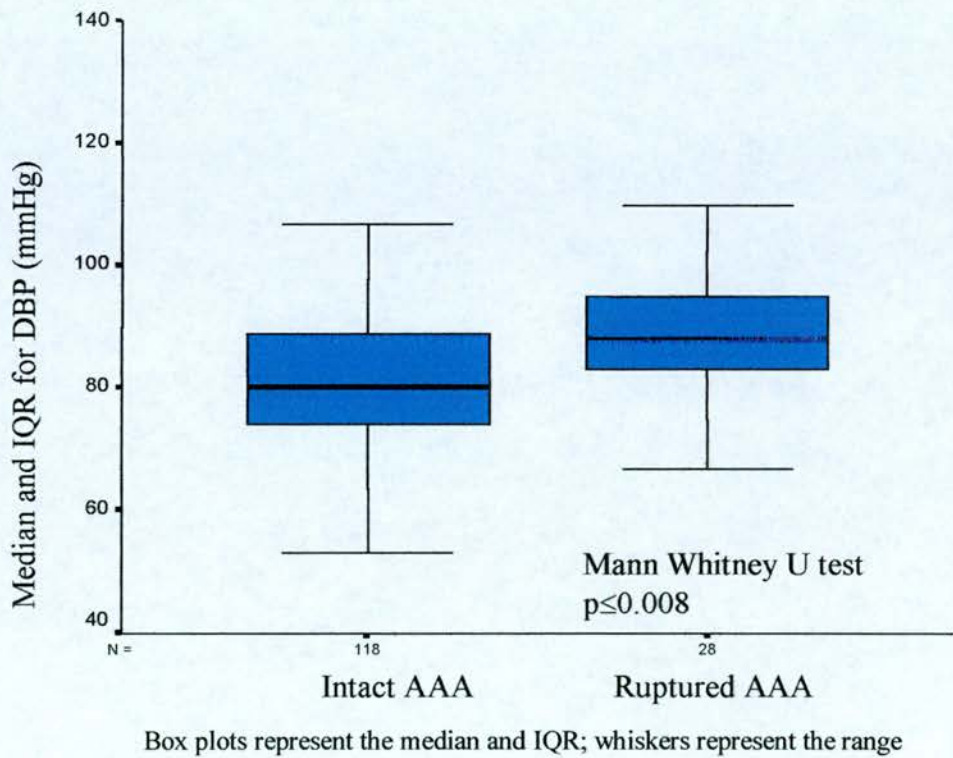


Figure 9.6. Differences in median (IQR and range) maximal aortic diameter between outcome groups at last follow-up.

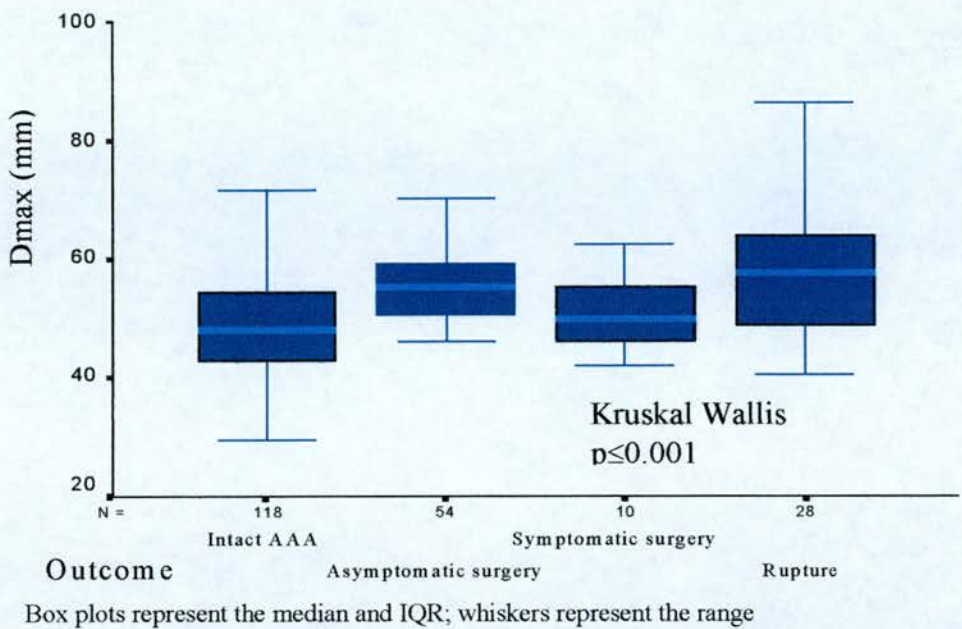


Figure 9.7. Differences in last follow-up maximal diameter between intact AAA and ruptured AAA categories.

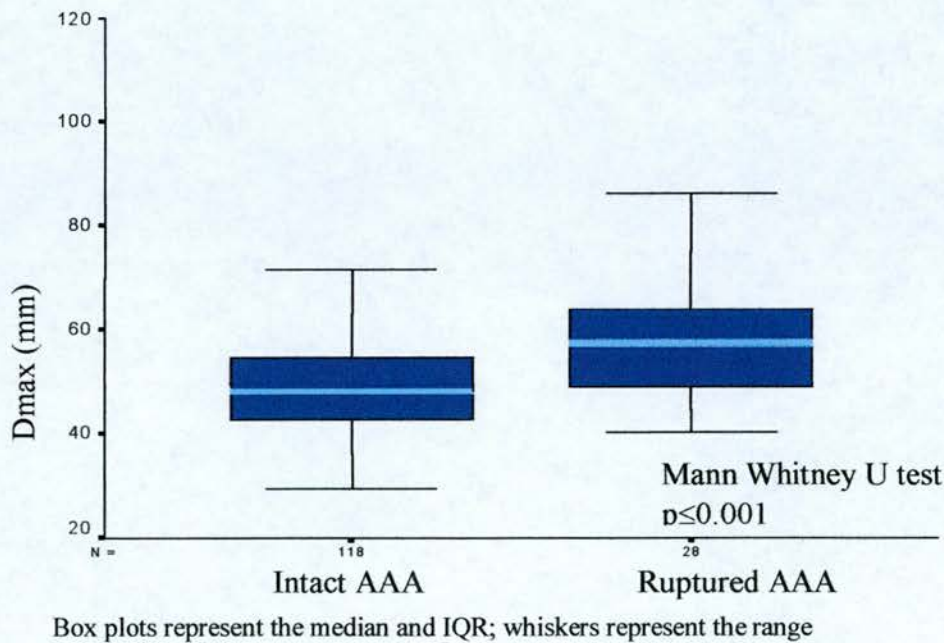
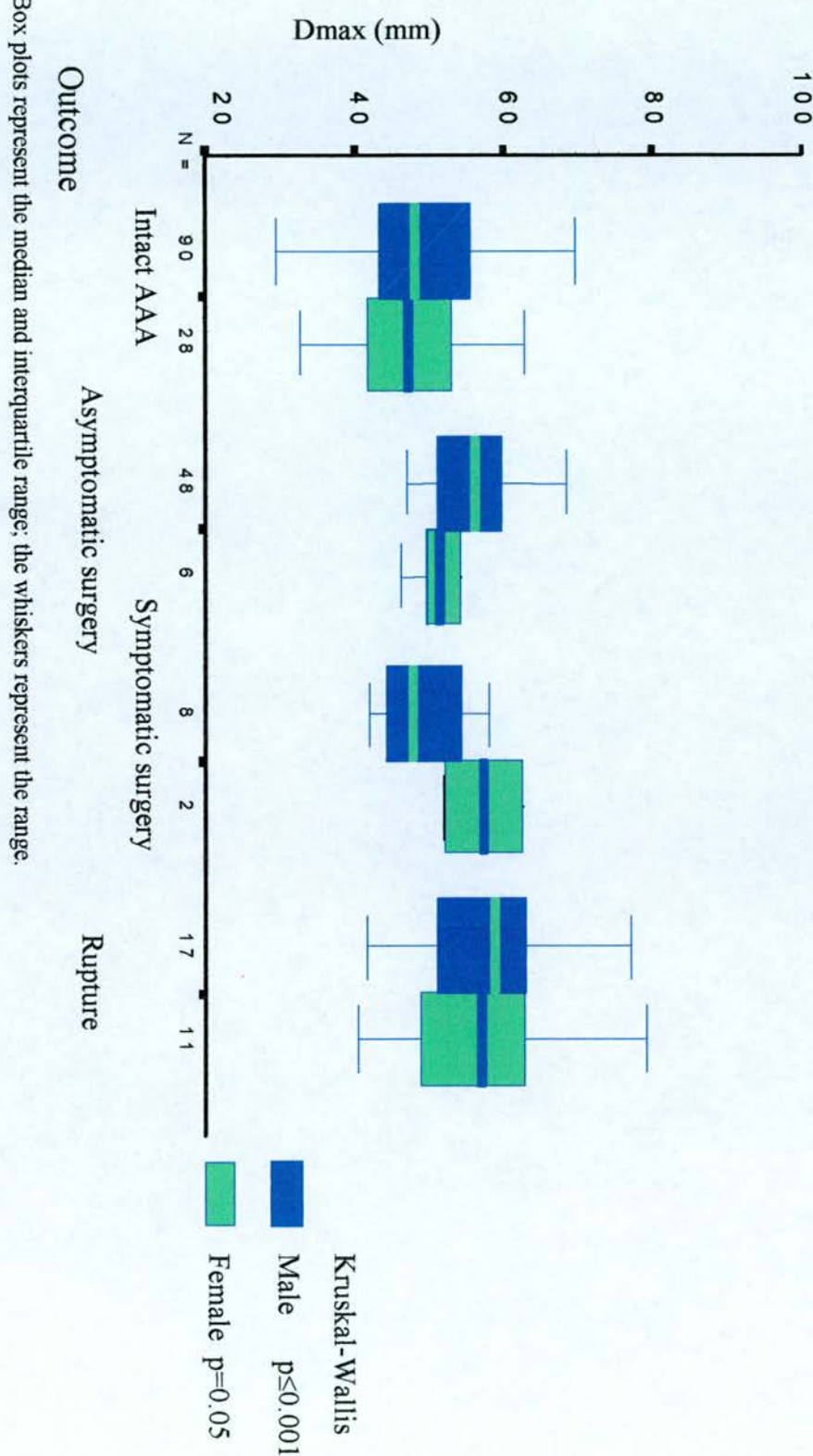


Table 9.4. Median (IQR) diastolic pressure and maximum diameter at last follow-up for 163 males and 47 females by outcome groups.

	Rupture	Elective symptomatic	Elective asymptomatic	Intact	Kruskal- Wallis, p
Males (n)	17	8	48	90	
DBP (mmHg)	89 (52-110)	72 (60-120)	84 (60-109)	80 (59-106)	0.012
Dmax (mm)	59 (42-114)	48 (42-58)	56 (47-102)	48 (30-80)	0.0001
Ep (10^5Nm^{-2})	3.53 (2.45-5.31)	2.92 (1.48-3.93)	3.28 (2.53-4.98)	3.52 (2.27-4.70)	0.481
β (a.u.)	23.2 (15.9-39.5)	20.0 (11.6-24.6)	22.1 (16.3-32.5)	22.9 (15.9-31.8)	0.618
Females (n)	11	2	6	28	
DBP (mmHg)	88 (67-120)	76 (75-78)	86 (68-92)	82 (53-116)	0.490
Dmax (mm)	57 (40-79)	57 (52-62)	51 (46-70)	47 (33-72)	0.054
Ep (10^5Nm^{-2})	2.75 (1.66-4.24)	4.34 (3.94-4.73)	2.88 (1.67-4.07)	3.16 (2.51-4.2)	0.352
β (a.u.)	18.6 (10.5-22.9)	30.3 (30.0-30.6)	19.8 (12.2-29.5)	21.3 (17.2-28.8)	0.139

Figure 9.8: Median (IQR and range) of maximum diameter according to gender and outcome group.



9.5 Summary

At last follow-up:

- Diameter, Ep and β had increased significantly.
- Diameter was no longer correlated with Ep or β .
- The correlation between diameter and distensibility in males at baseline was no longer evident.
- The rupture group were older, had higher diastolic blood pressure and had larger AAA diameter than the intact group.
- There were no significant differences in distensibility between the outcome groups.

9.6 Discussion

The average time between last follow-up and the outcome event was 3 months but this ranged from 2 days to 3 years. This may still have been too long to observe any changes in blood pressure, diameter or distensibility occurring immediately prior to rupture. In male patients at last follow-up, Ep and β were no longer related to diameter. This suggests that AAA progression may be associated with a change in the relationship between diameter and distensibility. In female patients, there was no such relationship either at baseline or last follow-up. This may reflect a difference in the structure of AAA in females. In other words, AAA in females may be more advanced in terms of wall degradation than AAA of similar diameter in males. This may also explain their increased propensity to rupture. Although the correlations between variables differed between the sexes, when the absolute values for each of the variables were compared there were no differences between the genders.

Diastolic pressure remained significantly higher in the rupture group compared with the intact AAA group while systolic, PP and MAP were not significantly different. This suggests that diastolic pressure may be an important determinant of the risk of rupture. The details of this relationship may become clearer in Chapter 11 (Cox analysis).

Finally, in order to fully investigate any differences between males and females whose AAA ruptured, last follow-up data were divided by outcome and gender. The picture remained the same in the group as a whole in that diameter and diastolic pressure were higher in the rupture group than in the intact group in males and females. However, diastolic pressure was not significantly different in the female ruptured AAA group, possibly because of small numbers. Distensibility was not significantly different between the outcome groups in either sex. This may suggest that the absolute value of E_p or β is not as indicative of risk of rupture as the relationship between diameter and distensibility or between relative change in E_p and β and rupture. These relationships will be investigated in Chapter 10.

9.7 Conclusions

There was no relationship between diameter and distensibility and no difference in distensibility between the outcome groups at last follow-up. The lack of relationship between diameter and distensibility in females, coupled with the evidence that females appear to suffer AAA rupture more frequently than men, suggests that diameter alone may not reflect the dynamics of advanced (structurally closer to rupture) AAA. The absolute value of distensibility is perhaps not as indicative of risk of rupture as the relationship between diameter and distensibility.

Chapter 10: The relationship between outcome and changes in AAA distensibility, diameter and blood pressure

10.1 Introduction

This chapter describes change in the measured variables between baseline and last follow-up, and penultimate and last follow-up in relation to outcome and gender.

Further details of the numbers of patients in each part of the analysis are given in Appendix III.

10.2 Change in variables from baseline to last follow-up by outcome

There were no relationships between outcome and change in SBP, Dmax or distensibility. There was a significant difference in median change in DBP between the outcome groups (Table 10.1).

10.3 Change in variables from penultimate to last follow-up

10.3.1 Change in variables from penultimate to last follow-up by outcome

To take account of the fact that the greatest change in diameter and distensibility may take place immediately prior to rupture, the differences between the penultimate and the last follow-up were examined. 163 subjects provided penultimate and last follow-up data. The median (IQR) time interval between the penultimate and the last follow-up was not statistically different (Mann Whitney $p=0.55$) between the rupture group [5.5 (2.7-17.3) months] and the intact AAA group [6.1 (2.6-27.8) months]. Change in variable per month was calculated, as the time intervals between the outcome groups were approximately the same. Rate of change in diameter and distensibility between penultimate and last follow-up was not related to outcome (Table 10.2).

Table 10.1. The median (IQR) absolute change in blood pressure, diameter and distensibility between baseline and last follow-up by outcome.

	All	RAAA	Symptomatic repair	Asymptomatic repair	Intact AAA	Kruskal-Wallis, p
n	154*	19	4	36	95**	
DBP (mmHg)	3 (-6 to 10)	4 (-2 to 20)	-8.5 (-13 to -4)	8.5 (-1 to 13)	1 (-8 to 7)	0.01
SBP (mmHg)	0 (-12 to 16)	10 (-16 to 18)	-13 (-25 to 5.5)	0 (-12 to 12)	0 (-12 to 16.5)	0.36
PP (mmHg)	-2 (-60 to 60)	0 (-32 to 60)	0 (-29 to 2)	-4.5 (-60 to 40)	-2 (-44 to 44)	0.47
MAP (mmHg)	2 (-37 to 46)	5.7 (37 to 46)	-13 (-15 to 2)	4 (-26 to 22)	1 (-36 to 36)	0.09
Dmax (mm)	4.8 (2.2 to 8.4)	5.1 (2.2-9.2)	4.2 (3.4-4.7)	6.1 (2.3 - 12.3)	4.7 (2 - 8.2)	0.72
Ep (10 ⁵ Nm ⁻²)	0.33 (-0.55 to 1.44)	0.47 (-0.22 to 1.93)	-0.6 (-1.5 to 0.37)	0.29 (-1.36 to 1.75)	0.34 (-0.55 to 1.22)	0.30
β (a.u.)	2.4 (-5.1 to 8.1)	5.3 (0.1-11.8)	-2.0 (-9.1 to 4.4)	-0.2 (-12 to 10.4)	2.5 (-5.1 to 7.8)	0.32

Values indicate the absolute change in each variable. *n= 155 for BP variables; **n= 96 for BP variables

Table 10.2. The median (IQR) change per month in blood pressure, diameter and distensibility between penultimate and last follow-up by outcome.

	All	RAAA	Symptomatic repair	Asymptomatic repair	Intact AAA	Kruskal- Wallis, p
n=	163*	20	5	37**	101	
DBP (mmHg)	0.26 (-0.67 – 1.68)	0.72 (-1.21 – 2.31)	-1.13 (-2.47 – -0.48)	0.93 (-0.35 – 3.21)	0.19 (-0.67 – 1.13)	0.02
SBP (mmHg)	0.34 (-1.47 – 2.65)	0.66 (-1.76 – 2.95)	-0.50 (-4.52 – 0.92)	0.00 (-2.50 – 1.72)	0.36 (-1.01 – 2.84)	0.34
PP (mmHg)	0.00 (-1.80 – 1.36)	0.33 (-0.89 – 1.34)	0.16 (-2.05 – 1.63)	-1.84 (-3.34 – 0.49)	0.17 (-1.21-2.19)	0.01
MAP (mmHg)	0.36 (-0.89 – 1.92)	0.70 (-1.74 – 2.39)	-0.62 (-3.15 – -0.16)	0.48 (-0.65 – 2.73)	0.31 (-0.94 – 1.53)	0.15
Dmax (mm)	0.27 (0.00 – 0.57)	0.18 (-0.01 – 0.98)	0.37 (0.12 – 0.38)	0.44 (0.07 – 0.77)	0.25 (0.00 – 0.45)	0.35
Ep (10 ⁵ Nm ⁻²)	0.03 (-0.16 – 0.20)	0.12 (-0.04 – 0.21)	-0.10 (-0.15 – 0.00)	-0.03 (-0.28 – 0.21)	0.03 (-0.15 – 0.20)	0.43
β (a.u.)	0.00 (-0.93 – 1.14)	0.17 (-0.61 – 1.61)	-0.23 (-0.68 – 1.14)	-0.17 (-1.84 – 1.11)	0.06 (-0.87 – 1.01)	0.60

*n=164 for BP variables; **n= 38 for blood pressure variables. Values given in units/month

10.3.2 Change in variables from penultimate to last follow-up by gender

There were no significant differences in the rate of change per month in any of the variables between males and females (Table 10.3).

10.3.3 Relationships between rate of change in diameter and distensibility

In order to investigate the hypothesis that diameter and distensibility may change at differing rates during AAA progression, the changes in these variables were correlated.

There were no statistically significant relationships between rate of change in diameter and rate of change in distensibility in intact or ruptured AAA (Table 10.4). There was a tendency for larger aneurysms to expand more rapidly but this did not attain statistical significance (Table 10.5). Rate of change in E_p and β did not appear related to aneurysm diameter.

Table 10.3. Median (IQR) rate of change in variables per month from penultimate to last follow-up by gender.

	Males	Females	Mann-Whitney test, p
n	122	41*	
DBP (mmHg)	0.24 (-0.67 – 1.59)	0.26 (-0.71 – 1.73)	0.78
SBP (mmHg)	0.17 (-1.37 – 2.62)	0.45 (-2.22 – 2.70)	0.89
PP (mmHg)	0.00 (-1.57 – 1.34)	0.00 (-2.90 – 1.59)	0.80
MAP (mmHg)	0.38 (-0.90 – 2.16)	0.28 (-0.92 – 1.67)	0.77
Dmax (mm)	0.30 (0.03 – 0.60)	0.12 (-0.04 – 0.54)	0.18
Ep (10 ⁵ Nm ⁻²)	0.04 (-0.17 – 0.22)	0.02 (-0.13 – 0.12)	0.63
β (a.u.)	0.07 (-1.30 – 1.42)	-0.05 (-0.72 – 0.79)	0.92

*n= 42 for BP variables

Table 10.4. Correlation between rate of change in diameter and rate of change in distensibility in the intact and ruptured AAA groups.

	Intact AAA		Ruptured AAA	
	Change in Ep (10 ⁵ Nm ⁻² /month)	Change in β (a.u./month)	Change in Ep (10 ⁵ Nm ⁻² /month)	Change in β (a.u./month)
Change in Dmax (mm/month)	r=0.17 p=0.09	r=0.19 p=0.06	r=0.22 p=0.35	r=0.09 p=0.70

Spearman’s rank correlation

Table 10.5. Median (IQR) rate of change in diameter and distensibility per month between penultimate and last follow-up by categories of diameter at penultimate follow-up.

Diameter category (mm)	n	Dmax (mm/month)	Ep (10 ⁵ Nm ² /month)	β (a.u./month)
30.0-44.8	54	1.85 (0.0-4.0)	0.20 (-0.96-1.12)	0.85 (-4.7 – 6.0)
44.9-53.6	55	1.1 (0.0 – 2.8)	-0.22 (-1.1 – 1.0)	-0.8 (-9.9 – 5.2)
53.7-109.9	54	2.1 (0.1 – 4.3)	0.32 (-0.6 – 1.7)	1.4 (-6.5 – 8.4)
p (Kruskal-Wallis)		0.37	0.43	0.51

10.4 Summary

Between penultimate and last follow-up:

- DBP increased at a higher rate in the rupture group than in the intact AAA group.
- The rate of change in SBP, Dmax and distensibility was not significantly different between the outcome groups.
- The rate of change in DBP and SBP, Dmax and distensibility was not significantly different between males and females.
- The rate and direction of change in distensibility was not related to Dmax or expansion.

10.5 Discussion

There was no difference between aneurysms that ruptured and those that remained intact with respect to change in diameter and distensibility. AAA in females did not differ from males in terms of change in diameter or distensibility, despite their higher relative risk of rupture. This lack of positive findings may have been due to the time interval from the last follow-up to the outcome event being too long to capture the changes leading to rupture. Although the change in each variable has been calculated per unit of time (month), the data cannot show whether the rate of change was consistent throughout the six-month period. It may be the case that those whose AAA ruptured had an increased rate of change in diameter and an altered rate of change in distensibility during only the very last part of this time period, for example, in the last week. If this were the case, a six-month follow-up interval may not be sensitive enough to detect anything less than the most marked changes in diameter and distensibility.

Patients with ruptured AAA had a significantly greater increase in DBP per month compared to those whose AAA remained intact. However, BP changes from minute to minute and while this analysis aimed to look at change over time it was not possible to determine whether BP was increasing consistently during this time period or had simply increased at the time of the last follow-up visit. The change in diastolic pressure over the 6-month interval between the follow-up visits was 4mmHg in the rupture group and 1mmHg in the intact group. This magnitude of difference in the rupture group may not reflect a real difference since the variability of BP measurement in this study was 5%. This equates to a difference of about 4mmHg for DBP of 80mmHg.

Dmax appeared to change at approximately the same rate between diameter categories while distensibility changed at the same rate but not in a consistent direction (Table 10.5). Whether distensibility changes rapidly in the immediate pre-rupture period remains unanswered at this point in the analysis. It was not clinically practicable to collect distensibility data more frequently, although what 'frequently enough' actually is in terms of days or weeks remains unknown. Optimal follow-up may be more frequent than every three months (outcome occurred, on average, three months after last follow-up) but this may not be acceptable to patients nor financially viable. The following stage of analysis attempted to answer the question of the effect of change in distensibility on the likelihood of rupture.

10.6 Conclusions

There was no association between distensibility and diameter, outcome or gender. Change in distensibility was not related to outcome. This may have been because the

time period between last follow-up and the outcome was too long to have detected rapid changes that may have occurred in distensibility immediately prior to rupture.

Chapter 11 Multivariate time-dependent analysis

11.1 Introduction

The central hypothesis to be tested in this study was that AAA rupture might be preceded by a detectable change in wall distensibility and that this might allow a better prediction of rupture risk on an individual patient basis than AAA diameter alone. A time-dependent, multivariate analysis model was therefore used (Cox proportional hazard model, Chapter 4.6).

11.2 Aims

Since the univariate analyses showed few significant relationships between distensibility and risk of rupture, it was possible that the absolute values of E_p and β were less important than the relative change in either variable over time. To investigate whether a measurable change in distensibility occurred prior to rupture, the statistical model had to take account of changes in each variable over time, including that between last follow-up and rupture.

11.3 Cox proportional hazard model - additional methodology

The Cox proportional hazard model was used to examine the relationships between the measured variables (DBP, SBP, MAP, PP, Dmax, E_p and β), co-morbidity, drug and smoking history, and rupture. Changes in each measured variable were created as separate variables, calculated by the difference between each follow-up visit per month, so the model accounted for time-dependent changes in the variables;

$\log(\text{variable at latest follow-up}) - \log(\text{variable at previous follow-up})$

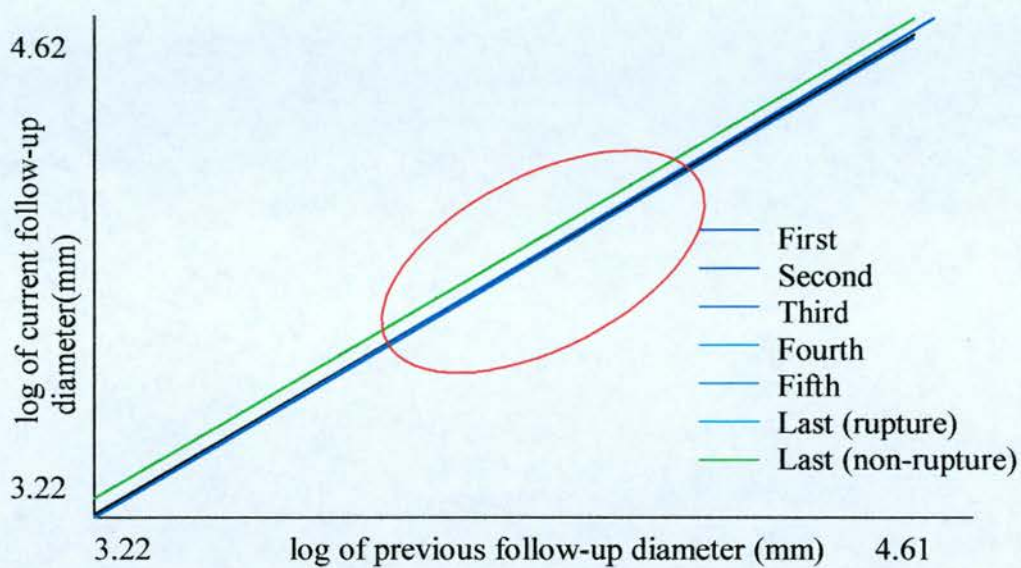
days between previous and latest follow-up $\times 30\text{days}$

11.3.1 Time-dependent estimation of data at outcome

Patient-specific risk estimation could not be derived directly from these data because the variables could not be measured at the time of rupture. The variability of AAA distensibility was high; more specifically, distensibility did not change at the same rate or in the same direction for any given patient or size of AAA. This meant that distensibility at the last follow-up was not necessarily representative of that at rupture or other outcome. In addition, several patients only contributed one data set, which prevented specific linear regressions being produced for them.

The Cox model, however, required an estimate of the change in the variables during the final time period. Diameter and distensibility at the time of outcome event were estimated from that measured at previous follow-up visits assuming a mean linear change. ‘Averaged’ linear regression models for each variable were produced and applied to the group as a whole using the following procedure. The log values of each variable at two sequential follow-ups (for example, Figure 11.1) were plotted against each other. Regression lines were plotted for each pair of data sets (e.g. baseline and follow-up 1) up to follow-up 5 to show the linearity of the relationships between the log values. Linear regression is the equation of the straight line ($y = a + bx$) that describes how a dependent variable (y) changes in relation to an independent variable (x). In this case, y = diameter at first follow-up, x = diameter at baseline follow-up, a = the value of y when $x=0$, b = the change in y per unit change in x .

Figure 11.1. Regression lines of maximum diameter between sets of current and previous follow-up data (visits 1-5), and estimated regression lines between diameter at last follow-up and at outcome in the rupture and non-rupture groups.



Red circle denotes the median points of the lines and shows their similarity at these points

In order to maximise the number of subjects contributing valuable data, while at the same time using the period closest to the outcome event, data from the median follow-up visit were used. Thus, the regression equation predicting the third follow-up variables from the second follow-up data was considered likely to be the most representative of the potential change occurring in diameter, E_p or β between the last follow-up and the outcome event. The use of averaged estimates may have diluted the significance of the magnitude and rate of change in the variables in the rupture group. However, actual measurement at the time of rupture was not possible.

The regression equations for diameter, E_p and β were calculated by the statistical analysis package and applied to the data at last follow-up producing an estimate of the data at outcome as follows: (* represents 'multiplied by')

1. Diameter at event = $\exp (1.0001328*\text{last f-up diameter} + 0.000162*\text{days between last follow-up and event})$
2. E_p at event = $\exp (0.860915*\text{last } E_p + 0.000589*\text{days})$
2. β at event = $\exp (1.005944*\text{last } \beta - 0.000080281*\text{days})$

11.3.2 Selection of the variables in the Cox proportional hazard model

Independent variables are those that explain or determine the value of the dependent variable, which in this case is time to rupture. The choice of which independent variables to test by the Cox proportional hazard model depends on a balance between including variables that may be associated with rupture while avoiding too large a number of variables, which would make interpretation extremely complex. Each variable chosen was analysed by the regression process (described below) but the final model included only those having a significant, independent effect on the dependent variable.

There is no method of variable selection that is preferable to another, so two (step-wise regression and the 'goodness of fit') have been used to allow a comparison.

- I. Stepwise regression involves repeatedly adding the most significant (or significant is arbitrarily defined, in this case $p \leq 0.10$) new variable to the existing model and removing variables that are no longer significant (in this case $p \geq 0.05$) following the addition of the new variable. Simple linear regressions are carried

out on each of the independent variables. The most significant variable equal to or below the 10% level is chosen and kept as the first variable. Multiple regression with two variables i.e. the selected variable and each of the other variables, is carried out and the two-variable regression model accounting for the lowest significance equal to or below the 10% level is selected. Variables that do not reach significance at the 5% level once in the model are removed. The process continues until all the variables have been tested and there are no more significant new variables to add. The final model consists of all of the significant, independent variables.

- II. The 'goodness of fit' method creates a regression model for every possible variable combination and produces the 'goodness of fit' statistic for each model. A list is produced of the 'best' model for each number of variables i.e. 'best' two variable model, 'best' three variable model, etc. A score is allocated to each variable combination. This score rises in increasing intervals with the number of variables included until the optimum variable combination occurs; thereafter the score increases by decreasing amounts. The variables producing the 'best' fit are taken to be those at the point just before the difference between the statistics becomes relatively smaller, thereby making it unnecessary to add another variable to the model (Table 11.4).

All continuous variables considered for the model were treated as such. The natural logarithms for all the variables, except age (which was normally distributed), were used because the distributions of the variables were skewed. Logarithms could not be

used for smoking data as some patients had never smoked and zero (pack-years) cannot be log transformed. The square root of pack-years was used instead.

11.3.3 Three models

Three models (A, B and C) were created; each was age and sex adjusted. The variables considered for the models included a combination of the following; DBP, SBP, MAP, PP, Dmax, Ep, β , claudication, pack-years smoked, chest pain, leg pain, angina score, MI, family history of AAA, coronary artery bypass surgery, beta blocker use. The specific variables used are detailed in the analysis of each model. Model A analysed the measured variables and time to rupture using stepwise regression while model B analysed measured variables, smoking, co-morbidity, drug use and time to rupture using the same method. Due to the complexity of the inter-relationships between the variables chosen for model B, the 'goodness of fit' method of final model selection, was carried out on the same variables (model C) to verify whether the results were borne out. Unlike stepwise regression, which composed the final model from the most significant variable at each step, the 'goodness of fit' method included the non-significant variables (Table 11.4) in each model and gave their significance levels.

11.3.4 Cox proportional hazard model output

Parameter estimate – In the linear regression equation $y = a + bx$, the parameter estimate is the slope 'b' for each variable i.e. the value 'b' applied to the respective variable 'x' to produce the regression equation.

Hazard ratio – (HR) This is a measure of the risk of rupture in those with the variable relative to those without the variable or with a different value for the variable. The magnitude of the increased or reduced rupture risk is the proportion of the hazard ratio above or below 1. For example, a HR of 1.5 equates to an increased risk of rupture of 50% (i.e. 1.5 x the risk) for a stated change in the original scale of ordinal variables or in comparison groups for categorical data. In this study the HR relates to a 10% change on the original scale of the variable, as opposed to the log scale:

Hazard ratio =1 – there is equal risk between the groups being compared.

Hazard ratio >1 – there is an increased risk of rupture (shorter time to rupture) in those patients with the variable of interest.

Hazard ratio <1 – there is a decreased risk of rupture (longer time to rupture) in those patients with the variable of interest.

Hazard function – this is closely related to the survival curve, representing the risk of dying (in this case, AAA rupture) in a short time interval after a given time, assuming survival thus far. The hazard function $H(t)$ can therefore be interpreted as the risk of rupture at time, t . Although a specific time period could not be attached to t , as will be seen in the models' results, it was possible to interpret it as a shorter or longer time period from the point of measurement to point of rupture. The Cox method uses the hazard function as its dependent variable; in other words, time to rupture was the dependent variable and the independent variables contributed to a longer or shorter time to rupture.

Cox proportional hazard model is of the form:

$$h(t) = h_0(t) \times \exp[b_1X_1 + b_2X_2 + \dots + b_pX_p]$$

Where $h_0(t)$ is the baseline or underlying hazard (when all variables are zero), b_i are the parameter estimates, and X_i are the explanatory/ independent variables. The cumulative hazard, $H(t)$ can be obtained by adding up the hazard over time 0 to t , i.e. sum of $h(i)$ over i from $i=0$ to $i=t$. The probability of surviving up to time t , $S(t)$ can be estimated by $\exp[-H(t)]$.

11.4 Results of Cox proportional hazard model analyses

11.4.1 Model A

Variables considered for entry into the model (all time dependent)

Age	Gender (male-1, female-2)
Log maximum diameter	Log change in β / month
Log E_p	Log diastolic pressure
Log β	Log systolic pressure
Log change in diameter/ month	Log mean arterial pressure
Log change in E_p / month	Log pulse pressure

These variables were those at each follow-up period and the change in D_{max} , E_p and β between each follow-up.

Variables entering the final model A

After adjusting for age and sex, gender, D_{max} , change in E_p and DBP achieved 5% significance and were included in the final model (Table 11.1). None of the other variables considered were significantly related to time to rupture.

11.4.2 Interpretation of model A

The increase in risk of rupture associated with female gender was 178% (HR 2.78) in comparison to males, suggesting that AAA in females were almost three times as likely to rupture as those in males of the same age, blood pressure, AAA diameter and change in Ep at any point in time. A 10% increase in diameter equated to a 36% (HR 1.36) increase in rupture risk at any point in time, when compared to no change in diameter. A reduction in proportionate change in Ep of 10% resulted in a 38% ($1/\text{HR} = 1.38$) increase in rupture risk in comparison to no change in Ep. Finally, a 10% increase in diastolic BP at any point in time equated to a 47% greater risk of rupture in comparison to no change in diastolic BP.

Table 11.1. Results of the stepwise procedure for model A

Variable	Parameter Estimate	Standard error (S.E.)	p-value	Hazard ratio (95% CI)
Age	0.0601	0.0374	0.1078	1.062 (0.997-1.143)
Sex	1.0241	0.4152	0.0136	2.785 (1.234-6.284)
Log (max diameter)*	3.2667	1.0588	0.0021	1.365 (1.120-1.663)
Log (change in Ep)*	-3.4161	1.3358	0.0105	0.722 (0.563-0.927)
Log (diastolic BP)*	4.0628	1.4149	0.0041	1.473 (1.131-1.918)

*Hazard ratio and associated confidence interval relates to a 10% change in original scale or category.
 Confidence intervals (CI) including 1.0 are not significant, CI completely above or below 1.0 are significant as reflected in the p-value.

11.4.3 Summary of model A

From this model, it can be concluded that the following variables led to a shorter time to rupture:

- Female gender.
- Higher maximum diameter.
- Higher diastolic blood pressure.
- Larger proportionate decrease in Ep.

11.4.4 Model B

Time dependent variables considered for entry into the model

Log maximum diameter	Log change in β / month
Log Ep	Log diastolic pressure
Log β	Log systolic pressure
Log change in diameter/ month	Log mean arterial pressure
Log change in Ep/ month	Log pulse pressure
Hypertension at each follow-up (definition in Chapter 4.4.3)	

Non time-dependent variables considered for entry into the model

- The square root of pack-years
- Chest pain
- Leg pain
- Angina score (grade 1 and 2 grouped together)
- Family history of AAA (father, mother or siblings)

Coronary artery bypass surgery

History of myocardial infarction or angina

Beta-blocker use at baseline

Diabetes

Variables entering the final model B

After adjusting for age and sex, gender, Dmax, and smoking achieved 5% significance and were included in the final model (Table 11.2). None of the other variables considered were significantly related to time to rupture.

11.4.5 Interpretation of model B

The increased risk of rupture associated with female gender in model B was 140% (HR 2.40). Interestingly, after adjusting for age, co-morbidity and smoking, a 10% increase in diameter led to a 60% (HR 1.60) increase in rupture risk which was higher than that in model A (36%). The hazard ratio of <1 for pack-years smoked suggests that patients who smoked less had a shorter time to rupture. This was not as expected.

Table 11.2. Results of the stepwise procedure for model B

Variable	Parameter Estimate	Standard error (S.E.)	p-value	Hazard ratio (95% CI)
Age	0.0414	0.0362	0.2525	1.042 (0.971-1.119)
Sex	0.8749	0.4236	0.0389	2.399 (1.046-5.502)
Log (max diameter)*	4.9360	1.0226	0.0001	1.601 (1.322-1.938)
Sqrt (pack-years)	-0.2263	0.0825	0.0061	0.797 (0.678-0.937)

*Hazard ratio and associated confidence interval relates to a 10% change in original scale of maximum diameter.

Sqrt – square root

11.4.6 Summary of model B

From this model it can be concluded that the following variables led to a shorter time to rupture:

- Female gender;
- Higher maximum diameter;
- Gender and age or inaccurate reporting may have confounded the effect of smoking. This is discussed further in section 12.5.

11.4.7 Model C

Using the ‘goodness of fit’ method, the optimal three-variable, four-variable, five-variable, etc. regression models selected were listed (Table 11.3).

Table 11.3. The ‘best’ of the 1-8 variable models using the ‘goodness of fit’ method of model selection.

DF [#]	Score	Variables included in the model
2	15.3	Age, sex - automatically included in all models
3	30.0	Maximum diameter
4	43.8	Change in Ep, change in β
5	58.2	Maximum diameter, change in Ep, change in β
6	66.0	Maximum diameter, change in Ep, change in β , pack-years
7	68.2	Maximum diameter, Ep, change in Ep, change in β , pack-years
8	69.9	Maximum diameter, Ep, change in Ep, change in β , diastolic blood pressure, pack-years

[#]Degrees of freedom = number of variables in the model.

Whilst the variables are referred to on their original scale, the natural logarithms of these variables were added to the model (except for age, sex and the square root of pack-years).

Variables entering the final model C

After adjusting for age and sex, repetitively adding one more variable to the model increased the score statistic of the best model by 14.9, 13.6, 14.7, 7.8, 2.2 and 1.7 respectively. The score value increased by 7.8 between the five- and six-variable models but only by 2.2 between the six- and seven-variable models. The score value did not increase markedly by adding a seventh or eighth variable, and so the most appropriate model using this method of variable selection was probably the six-variable model. This included gender, Dmax, proportional change in E_p and β , and pack-years smoked.

Table 11.4. Results of the 'best fit' analysis for model C.

Variable	Parameter Estimate	Standard error (S.E.)	p-value	Hazard ratio (95% CI)
Age	0.0419	0.0373	0.2622	1.043 (0.969-1.122)
Sex	0.8203	0.4352	0.0594	2.271 (0.968-5.329)
Log (max diameter)*	3.9187	1.1256	0.0005	1.453 (1.177-1.793)
Log (change in Ep)*	-3.8754	1.8652	0.0377	0.691 (0.488-0.979)
Log (change in β)*	4.6392	3.1045	0.1351	1.556 (0.871-2.779)
Sqrt (pack-years)	-0.2272	0.0844	0.0071	0.797 (0.675-0.940)

Model chi-square 52.2 with 6 d.f., $p < 0.0001$

*Hazard ratio and associated confidence interval relates to a 10% change in original scale of variables.

Sqrt- square root

11.4.8 Interpretation of model C

Female gender was associated with 127% (HR 2.27) higher rupture risk than male gender although this was just non-significant; a 10% increase in Dmax was associated with a 45% increase in rupture risk; a 10% reduction in Ep was associated with a 45% higher risk of rupture and lower value of pack-years smoked was associated with a 26% increased risk of rupture. This finding is difficult to explain and is further discussed in section 12.5.

11.4.9 Summary of model C

From this model, it can be concluded that the following variables led to a shorter time to rupture:

- Female gender
- Higher maximal diameter
- Lower proportional change in Ep
- Higher number of pack-years smoked [may have been confounded or biased (section 12.5)]

11.5 Discussion

Model A examined the relationship between the measured variables and risk of, or time to, rupture. It did not take into account the effect of co-morbidity, risk factors or drug therapy. Model A was, therefore, viewed as a haemodynamic model of AAA rupture risk, which might be sufficiently simple for clinical use in the out-patient department and the final conclusions of this thesis have been taken from this model. However, the presence of angina and claudication indicate the presence of atherosclerosis, and it is possible that aortic atherosclerosis may have an effect on

AAA expansion and rupture. Smoking has also been implicated in rupture risk (Brown and Powell 1999). The aim of models B and C, therefore, were to assess risk of rupture while adjusting for these non-measured variables, despite the risk of obscuring interpretation by including a higher numbers of variables.

Two methods of variable selection were used on the same data in recognition of the fact that there is no preferred method and to allow the results of B to be verified, or otherwise, by C. It may be that stepwise regression in model B used such a rigorous method of final variable selection that variables with a bearing on rupture risk were excluded. In which case the 'goodness of fit' method, producing model C, may give a broader picture of factors impacting on rupture risk. Models B and C were more complex to interpret because of the inclusion of smoking, drug and medical histories. The difficulties inherent in their inclusion are discussed in Chapter 12.

Age was not significantly related to risk of rupture in any of the models. It seems likely that this can be explained by the close relationship between diameter and age, where diameter may have a stronger association with time to rupture than age. However, the higher relative risk of rupture (2.65) in the 80-89 year age group compared with the 70-79 year age group suggests that age may remain an important factor in rupture risk (see Chapter 12).

Female gender and higher Dmax were related to increased rupture risk in all three models and require little further discussion. Suffice to say that females of the same age, and with the same AAA diameter and blood pressure, as males may benefit from

earlier AAA repair. The findings for diastolic blood pressure, proportional change in Ep and smoking habit require further explanation.

Model A showed that after adjusting for the other measured variables, DBP continued to have an independent, significant impact on rupture risk. DBP was not included in the final models B and C. The significant relationship between DBP and time to rupture in model A may have been confounded or replaced in models B and C by smoking status. Model A suggested that higher DBP related to shorter time to rupture, while model B suggested that lower pack-years smoked related to a shorter time to rupture. If smoking status were confounding the effect of DBP, those with lower pack-years smoked would also have higher DBP. However, the Kruskal-Wallis test showed that there were no significant differences in DBP between tertiles of pack-years smoked ($p=0.104$). Nevertheless, the result is approaching statistical significance. Pack-years may have had some level of confounding effect on DBP. It was not possible to determine exactly why DBP was no longer significantly related to time to rupture from these data. Further analysis of the impact of DBP on rupture risk would require more detailed (more frequent) collection of blood pressure and drug data.

Previous workers investigating the relationship between AAA rupture and blood pressure found that $DBP > 105 \text{ mmHg}$ was significantly associated with increased risk of rupture (Cronenwett 1996). Vardulaki *et al* (2000) found that diastolic 'hypertension' ($DBP > 100 \text{ mmHg}$) was significantly related to the occurrence of AAA; whereas raised SBP, MAP and PP were not. The UKSAT found that MAP was independently associated with increased rupture risk. It was not clear whether DBP was actually tested. Thus, it has been concluded that model A's finding that DBP

(>90mmHg) was significantly associated with an increased risk of rupture, independently of age, gender, AAA diameter and distensibility, supports previous findings. In AAA surveillance, recording DBP in addition to diameter may enhance the accuracy of rupture risk prediction.

Proportionate change in Ep was significantly related to rupture in models A and C, but not in B. The non time-dependent variables may have interacted in some way to make change in Ep and β non-significant at the 5% level. The equation to calculate the log change in Ep per month was:

$$\frac{\log(\text{latest Ep}) - \log(\text{previous Ep})}{\text{Days between measurements}} \quad \times 365.25/12$$

$$\Rightarrow \frac{\log(\text{latest value/previous value}) \times 365.25/12}{\text{Days between measurements}}$$

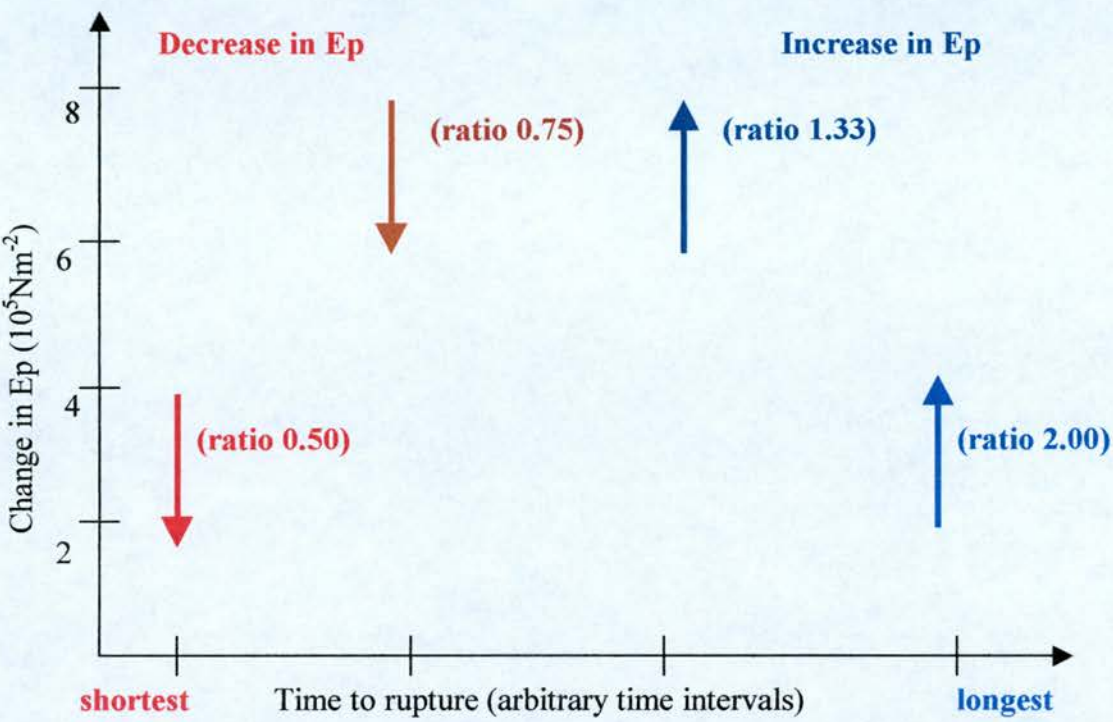
$$\Rightarrow \log(B) - \log(A) = \log(B/A)$$

Where A is the previous value and B is the latest value of the variable.

Thus log change in Ep is actually the proportionate change in Ep over time. If the change in Ep is an increase, the log (B/A) ratio is higher than that produced by a decrease in Ep of the same magnitude (Figure 11.3).

The hazard ratio (and 95% CI) for relative change in Ep was less than one in models A and C, suggesting that those whose AAA continued to increase in Ep (decrease in distensibility) had a longer time until rupture and therefore a lower risk of rupture. Those patients whose AAA Ep began to reduce (increasing distensibility) were more likely to rupture within a shorter time.

Figure 11.3: The relationship between the change in E_p [ratio of this change = \log (latest E_p /previous E_p), and time to rupture in model A.



It would appear from these data that distensibility could theoretically be of use in rupture risk prediction if the reasons for its high variability could be understood. It is also clear that follow-up would have to be more frequent than that employed by this study to ensure ‘capture’ of the changes in distensibility which may indicate imminent rupture.

The hazard ratio of <1 for pack-years smoked in models B and C suggests that patients who smoked less had a shorter time to rupture. This finding was not expected, but it is

possible that this was due to confounding. Females in this population smoked fewer cigarettes but had a higher relative risk of rupture and shorter time to rupture. This may have led to an erroneous association between low pack-years smoked and reduced time to rupture. Additionally, older patients smoked fewer cigarettes in this study but had a higher relative risk of rupture (Chapter 12) and tended towards a shorter time to rupture (model A and Chapter 12).

Beta-blocker use, the presence of hypertension and concomitant disease i.e. angina, MI or claudication, were entered into models B and C. However, none had a significant influence on time to rupture. From a statistical point of view, it is accepted that different combinations of variables considered by the regression model could produce different final model combinations. The complexity of the relationship between the variables means that changing just one variable within the group may lead to quite different variable interdependence becoming significant.

Despite these factors, significant results have been produced with regard to AAA distensibility. These results suggest that a larger proportionate decrease in E_p at any point in time indicates a shorter time to, or higher risk of, rupture. A reduction in E_p equates to an increase in AAA distensibility. It is possible that, immediately prior to the final breakdown of AAA wall matrix, AAA wall distensibility may increase (E_p decrease) because the tensile strength of the wall has finally been lost, and this leads rapidly to rupture. Observing distensibility at the same time as diameter may enhance understanding of wall matrix integrity, which may not be indicated by diameter measurement alone.

11.6 Conclusions

It would appear that the following variables act independently to reduce the time to rupture (increase the risk of rupture): female gender; larger diameter; higher diastolic blood pressure; and a larger proportionate decrease in E_p (an increase in distensibility).

Chapter 12. The relationship between factors associated with vascular disease and AAA distensibility

12.1 Introduction

The factors associated with vascular disease and AAA that have been investigated in this study fall into three categories:

- Risk factors for AAA - Smoking
Hypertension
Family history
- Indicators of atherosclerotic disease - Angina
Myocardial infarction (MI)
Coronary artery bypass graft (CABG)
Claudication
- Hypertensive/ cardiac drug therapy - Angiotensin converting enzyme (ACE) inhibitors
 β - adrenoceptor antagonists (blockers)
Calcium (Ca) channel blockers

The risk factors for AAA formation are well described and have been discussed in Chapter 1. Briefly, male gender, age, smoking and hypertension increase the risk of AAA formation (McSweeney *et al* 1994a, Cronenwett 1996, Lee *et al* 1997, Lederle *et al* 1997 and Wilmink *et al* 1999). The presence of atherosclerotic disease does not

appear to directly increase the occurrence of AAA or rupture but may be indirectly associated with the progression of AAA disease.

β -blockade, calcium channel blockade and ACE inhibition increase arterial wall distensibility directly by influencing arterial smooth muscle behaviour and indirectly by reducing blood pressure (Bank 1997, Englund *et al* 1998, Topouchian *et al* 1999). As these anti-hypertensive drugs affect vascular tone, their relationship with AAA expansion and rupture has been investigated. This chapter aims to explore the relationships between the above factors and AAA wall distensibility, diameter, expansion and rupture risk.

12.2 Additional methodology

Smoking has been divided into tertiles of pack-years. Pack-years were calculated by the number of smoking years x number of cigarettes per day/ 20. Ten patients had never smoked but this was deemed too small a number to compare between two outcome categories (rupture or intact AAA); the division into tertiles of pack-years avoided confounding by small numbers. A number of patients had recently changed their smoking habits dramatically from a large number of cigarettes to a small number of cigars or tobacco. In these cases the current smoking habits have been ignored in favour of the level of exposure to smoking (pack-years).

12.3 Results

There were several anomalies in the co-morbidity data collected. For example, although 61 (30%) subjects claimed to have had an episode of severe chest pain lasting more than 30 minutes, 4 stated that the cause was unknown, 32 stated angina

to be the cause and 64 stated that they had had a myocardial infarction (MI). Some subjects claimed not to have had chest pain but did think they had either angina or had had an MI. Although some patients may have had asymptomatic MI, it is also likely that some subjects gave inaccurate histories.

12.3.1 Prevalence of the factors associated with arterial disease within the study population.

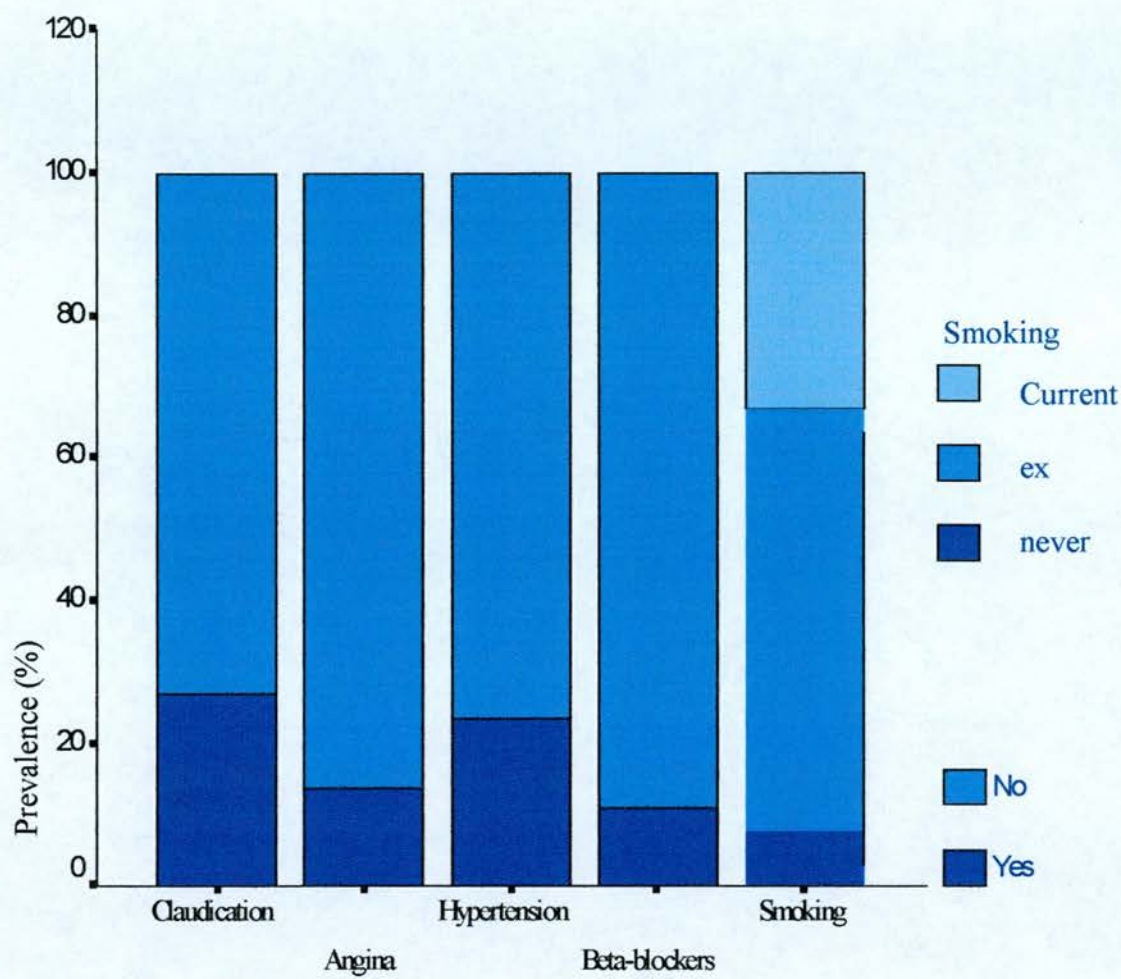
Table 12.1 describes in detail the prevalence of the factors described above in the study population. The data were collected at baseline and the results given here are for the 210 subjects who produced usable data at any point in the follow-up. As can be seen, the majority (>70%) did not have angina or claudication (Figure 12.1). In spite of the low numbers with cardiac or peripheral vascular disease, 95% gave a history of smoking. Self-reported smoking history is however, susceptible to inaccuracies (Brown *et al* 1999). Few had diabetes and there was a rather low family history of AAA in the immediate family members. This latter finding should be viewed bearing in mind the inaccuracies inherent in anecdotal evidence regarding death from AAA of these elderly subjects' parents and siblings.

Table 12.1. Prevalence of risk factors for AAA disease in the study population at baseline where n= 210. [n (percent of population)]

Risk factors and associated factors	Yes	No	Missing (reason)
Angina	Grade 1 14 (7%) Grade 2 13 (7%)	171 (86%)	12 (2 - poor memory 10 - inaccurate pain description)
Severe chest pain	61 (30%)	147 (71%)	2 (poor memory)
MI	59 (28%)	149(72%)	2 (poor memory)
CABG	31 (15%)	178 (85%)	1 (no notes)
Claudication	55 (29%)	150 (84%)	5 (not mobile)
Hypertension	46 (24%)	147 (76%)	17 (no baseline clinical data)
Hypertension therapy	84 (40%)	124 (60%)	2 (poor memory)
β-blockers	16 (8%)	194 (92%)	—
ACE inhibitors and/ or Ca channel blockers	57 (27%)	153 (73%)	—
Smoking	Current 70 (34%) Ex 129 (62%)	Never 10 (5%)	1 (poor memory)
Pack-years	Median 38 (IQR 20-54)	—	1 (poor memory)
Diabetes	12 (6%)	196 (94%)	2 (poor memory)
Family history	Father 2 (1%) Mother 0 Brother 5 (2%) Sister 2 (1%)	199 (96%)	2 (poor memory)

CABG- coronary artery bypass graft. All information was self-reported

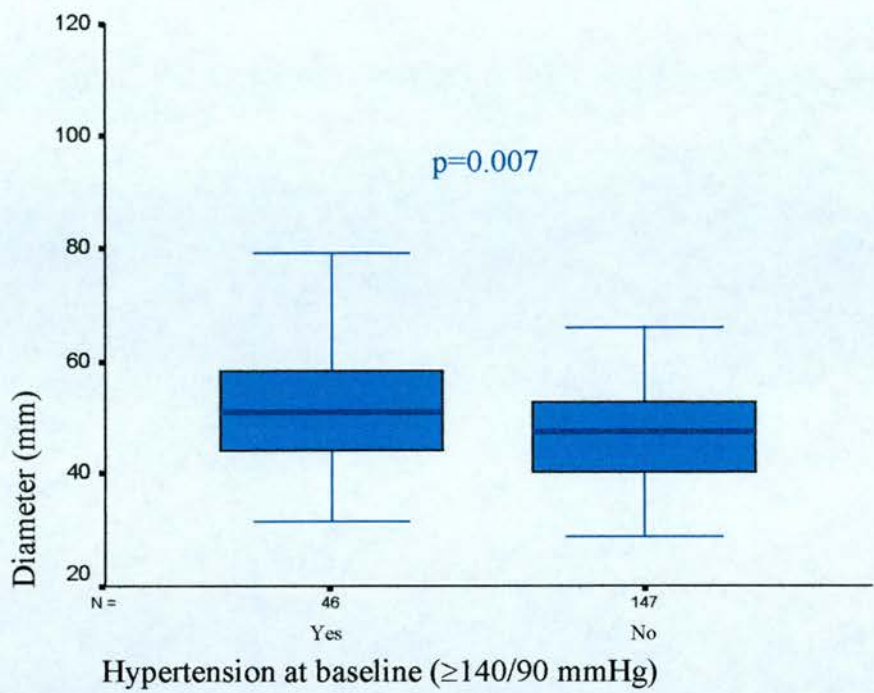
Figure 12.1. The prevalence of atherosclerotic disease, hypertension, pack-years smoked and β -blocker use in the study population.



12.3.2 The effect of associated factors on AAA diameter and distensibility.

Age, diameter and distensibility in those with and without the associated factors were compared. There were no significant differences in AAA diameter or distensibility between those with angina, claudication, ACE inhibitor, Beta-blocker or Ca-channel blocker therapy, diabetes, nor in current or ex-smokers when compared with those who did not have the above factors or who had never smoked ($p \geq 0.15$). Age was not significantly different between those with and without hypertension, although diameter was. At baseline, diameter was higher in hypertensive subjects than normotensive subjects but distensibility was no different (Figure 12.2 and Table 12.2). The difference in age between those with any of the above factors and those without are detailed in Table 12.2. The non-significant results are not given in Table 12.2.

Figure 12.2. Differences in AAA diameter in subjects with and without hypertension.



Boxplots represent the median, interquartile range and range of values. p-value using Mann-Whitney U test.

Table 12.2. Significance levels for differences in age and maximum diameter where significance was reached between those with the associated factor and those without.

Risk factor (% with factor)	Variable	Median (with risk factor)		Median (without risk factor)	p value
Hypertension (24%)	Diameter (mm)	51		47	0.007
Antihypertensive drugs	Age (years)	β- blockers (8%) 67	ACE inhib Ca channel blockers (27%) 72	None (65%) 74	0.025
Smoking (current 34% ex 61% never 5%)	Age (years)	Current 71	Ex 74	Never 77	0.016*
Diabetes (6%)	Age (years)	69		73	0.04

p-values using Mann-Whitney test except *Kruskal-Wallis test

12.3.3 Relative risk (RR) of AAA rupture in those with the associated factors.

The relative risk (RR) of AAA rupture in females was more than twice that of males. The relative risk of rupture in the 50-69 years age group was lower than that of the 70-79 year age group but the difference was not significant (95% CI 0.18-3.75). The RR of the 80-89 year group was more than twice that of the middle age group and this was significant (Table 12.3). Smoking was analysed in ‘current, ex and never’ categories. However, since there were only 10 subjects in the reference category (never smoked) the confidence intervals for the other two groups were very large and

non-significant (CI included 1). Smoking was subsequently analysed in tertiles of pack-years, which produced the unusual result of a significantly reduced RR in those in the upper tertile of smoking habit i.e. those who smoked most. The RR of rupture in the middle tertile was not significant. History of a coronary artery bypass graft appeared to be related to a reduced RR of rupture while hypertension doubled the risk. The presence of angina, claudication, antihypertensive therapy or family history had no significant relationship with risk of rupture.

In summary, female gender, age over 80 years and hypertension at baseline (systolic >140 mmHg, diastolic > 90 mmHg, Chapter 4) were the only factors which significantly increased the risk of rupture and which were unconfounded by other factors (see below). Diameter has been examined in Chapters 9-11.

No factor significantly altered the likelihood of operative repair. However, female gender tended toward a reduced likelihood of surgical repair but did not attain statistical significance. CABG and family history of AAA both tended toward increasing the likelihood of repair but neither reached statistical significance.

Table 12.3. Relative risk (RR) of AAA rupture and operative repair in those with the associated factors compared with those without.

Baseline risk factor (n=210)		Rupture RR (95% CI) (n=28)	Operation RR (95% CI) (n=69)
Male		1.00	1.00
Female		2.24 (1.55-3.26)	0.66 (0.43-1.01)
Age	70-79 years	1.00	1.00
	50-69 years	0.44 (0.18-3.75)	1.25 (0.75-2.09)
	80-89 years	2.65 (1.88-3.75)	0.74 (0.13-4.08)
Smoking	never	1.00	-
	ex	2.76 (0.82-9.34)	-
	current	1.91 (0.11-32.88)	-
Pack-years	Min 0-26	1.00	1.00
	Med 27-46	0.61 (0.22-1.66)	0.86 (0.17-4.28)
	Max 47-192	0.38 (0.21-0.68)	0.94 (0.00-∞)
Angina		1.15 (0.00-∞)	1.13 (0.01-∞)
CABG		0.22 (0.05-0.90)	1.46 (0.97-2.2)
Claudication		0.95 (0.00-∞)	0.84 (0.31-2.30)
Hypertension		2.01 (1.22-3.32)	0.88 (0.09-8.69)
Antihypertensive drugs		0.64 (0.00-∞)	1.05 (0.00-∞)
Family history		0.36 (0.00-∞)	1.73 (0.71-4.21)

RR=1 is comparison group. If none given, comparison is with those without the factor.
 RR>1 indicates higher risk of occurrence; RR<1 indicates lower risk of occurrence. ∞ = infinity.
 95% CI - if this includes 1 result is not significant. Significant values in bold.
 The rupture and operative groups were not exclusive, 5 ruptures were operated.

12.4 Summary

- Female gender, age over 80 years and hypertension ($BP \geq 140/90$) increased the risk of rupture.
- Hypertension was associated with increased AAA diameter and Ep but had no significant relationship with β .
- Indicators of atheromatous disease (angina and claudication) did not alter risk of rupture nor AAA diameter or distensibility.
- A greater number of pack-years smoked reduced RR of rupture but was confounded by two factors, namely; females and elderly smoked less but suffered ruptured AAA more.
- Smoking did not alter diameter or distensibility.
- Use of antihypertensive drugs did not appear to effect an alteration in diameter or distensibility in this study group.

12.5 Discussion

With the exception of the UKSAT (Brown and Powell 1999), few studies have investigated risk factors for rupture. As a result some comparisons have had to be made with risk factors for AAA occurrence instead of rupture. This study was not designed specifically to investigate the influence of these risk factors. However, information on co-morbidity, drug, smoking and family history were collected and their relationship with AAA distensibility and rupture analysed.

Angina and claudication:- Atheromatous plaque within the AAA wall may lead to altered wall mechanics and consequently altered response to pressure and diameter change. In this study, angina and claudication were used as indicators of

atherosclerosis to assess whether this disease process would affect AAA expansion or risk of rupture. Englund *et al* (1998) found cardiac disease (defined as angina, MI, cardiac intervention or ECG evidence) to be significantly related to higher AAA growth rate. Although no explanation has been offered as to the mechanism, it is possible that patients with claudication and angina may be more likely to develop atheromatous plaque within the aorta as well as the lower limb and coronary arteries. However, Naydeck *et al* (1999) found that atheromatous plaque was present in the aorta in 89-96% of AAA subjects and that the plaque was significantly larger than in those without AAA. This high percentage of atheromatous plaque in AAA could prevent any distinction, in terms of diameter or distensibility, between those with and without angina and claudication.

Table 12.2 shows that there were no significant differences in age, diameter, E_p or β between those with angina or claudication and those without. Table 12.3 shows that the RR of rupture in those with angina or claudication was not significant i.e. there was no difference in risk of rupture in those with or without angina or claudication. Patients who had undergone CABG had a lower RR of rupture but these subjects may have died of other causes before rupture could occur. It would appear, therefore, that in this group of subjects the presence of angina or claudication did not affect wall distensibility, nor were these subjects different in age, aortic diameter or risk of rupture to those without angina or claudication.

Smoking:- Smoking is the most important avoidable risk factor for AAA development (Brown and Powell 1999, Vardulaki *et al* 2000). Wilmink *et al* (1999) suggested that although smoking results in elastolysis, which may be important in

AAA formation, once significant widening has occurred, abnormalities in collagen metabolism (which are less obviously smoking related) might be more important for disease progression. This implies that a change in smoking habit after AAA formation is unlikely to affect AAA progression. In contrast, MacSweeney *et al* (1994b) suggested that smokers have higher growth rates than ex-smokers and that smoking increases the likelihood of AAA death. This is supported by the findings of the UKSAT (Brown and Powell 1999), which showed that current smokers had an increased risk of rupture compared with ex-smokers. Smoking status in the UKSAT was determined by measuring plasma cotinine levels. Brown and Powell (1999) found that self-reported smoking status was not significantly associated with survival (non-rupture). The present study did not collect cotinine levels and so had to rely on self-reported smoking status. The confounding effects of inaccurately reported smoking habit cannot, therefore, be underestimated and are likely to have played a role in the inexplicable finding of a lower RR of rupture in those who smoked most. Rather than this group of people having overestimated their smoking habit, it is more likely that those who claimed never to have smoked or to have stopped had not in fact done so.

In this study population, those who had never smoked were significantly older than the smokers (Table 12.2) but diameter, E_p and β were not significantly different.

When smoking status was divided into tertiles of pack-years there remained no significant differences in diameter, E_p or β between the groups. Table 12.3 shows that smoking 47-192 pack-years (the upper tertile) carried a reduced RR of rupture compared with smoking 0-26 pack-years (the lower tertile). To investigate whether this finding was due to heavy smokers dying of other diseases, the proportion of deaths between the smoking tertiles was compared. There were no significant

differences in the number of deaths in each group ($p=0.46$) or in the number of ruptures in each group ($p=0.32$).

Although this finding suggests that those who smoked least had a shorter time until rupture, several characteristics of these subjects may have led to confounding of the smoking data. Females smoked less than males [median (IQR) pack-years 30 (20-40) and 40 (20-59) respectively, $p=0.01$] but were more likely to suffer AAA rupture (RR 2.24). Older subjects also smoked less (Spearman's rank correlation $r = -0.19$, $p=0.006$ and median ages in each pack-year tertile, $p=0.016$, Table 12.2) but were, again, more likely to suffer AAA rupture (RR 2.65).

Hypertension:- Hypertension has been shown to be related to increased AAA expansion and rupture with diastolic pressure being a more accurate predictor than systolic pressure (Cronenwett 1996, Englund *et al* 1998, Vardulaki *et al* 2000). In Cronenwett's (1996) review it is suggested that hypertension is present in a higher percentage of rupture cases than non-rupture cases, and that more patients with hypertension subsequently rupture than those without hypertension. In view of the findings that a reduction in blood pressure increases aortic distensibility (Bank 1997), it can be assumed that hypertension results in reduced distensibility.

Maximum AAA diameter and E_p were significantly higher in those who were hypertensive at baseline. β was no different between the two groups. This supports previous reports that hypertension increases expansion (Cronenwett 1996, Englund *et al* 1998) and reduces distensibility (Naydeck *et al* 1999). It also supports the view that β is less pressure dependent than E_p (Reneman and Hoeks 1995). The relative risk of

rupture in the hypertensive was twice that of the normotensive subjects (this was significant) again supporting the studies discussed above.

Drug therapy:- It is now generally accepted that beta-adrenoceptor antagonists (β -blockers) increase aortic distensibility by a combination of blood pressure reduction and smooth muscle relaxation (Savolainen *et al* 1996, Bank 1997, Englund *et al* 1998). Ca channel blockers reduce vascular smooth muscle contractility resulting in vasodilation; ACE inhibitors reduce vasoconstriction and both result in lowered BP. As a result of both lower BP and relaxed SMC, aortic distensibility is increased following Ca channel blocker and ACE inhibitor use (Bank 1997, Slama *et al* 1995, Topouchian *et al* 1999). For this reason, those taking β -blockers, Ca channel blockers and ACE inhibitors have been grouped together and compared with those taking none of the above and where β -blockers alone have been analysed the comparison group excluded those taking ACE and Ca channel blockers.

Those taking β -blockers, ACE inhibitors and Ca channel blockers were significantly younger than those taking none of the three aforementioned drugs (Table 12.2).

However, use of these three drugs did not significantly alter diameter, Ep or β . It is possible that AAA in those on antihypertensive therapy were picked up at an earlier age simply because of contact with the medical profession. If this was the case, diameter might also be expected to be smaller in the group using antihypertensive therapy than in the non-treated group. In fact, diameter was not significantly different. This suggests that the subjects using any of these three drugs (who had been, therefore, hypertensive for a period of time) developed AAA at an earlier age than taking no antihypertensive medication. These data do not clearly support previous

findings of altered diameter and distensibility with beta-blocker use (Savolainen *et al* 1996, Bank 1997, Englund *et al* 1998), but this may be because of the small numbers taking β -blockers (n=16). Use of any of the three drugs did not significantly alter RR of rupture (Table 12.3), nor did β -blockers alter time until rupture after adjusting for age, sex, diameter, distensibility, smoking, concomitant atherosclerotic disease and pack-years (Chapter 13, model B).

Although these results may appear somewhat inconclusive regarding the effect of β -blockers, ACE inhibitors and Ca channel blockers on AAA wall distensibility, this reflects the fact that this study was not specifically designed to address this issue.

More detailed drug history, including changes in drug use over time and blood levels of each drug at the time of distensibility measurement, may be necessary to clarify the relationship between antihypertensive therapy and AAA distensibility.

12.6 Conclusions

Female gender, age over 80 years and hypertension (BP \geq 140/90) increased the risk of rupture, but indicators of atheromatous disease (angina and claudication) did not. The relationship between smoking and risk of rupture may have been confounded in this study by inaccurate self-reporting, and by the influence of age and gender.

Chapter 13. Discussion of findings

13.1 Introduction

The aim of this study has been to test the variability of distensibility measurement in AAA, to observe and describe the distensibility of the AAA wall, and to describe the relationships between distensibility, diameter and risk of AAA rupture. The aims and objectives are described in Chapter 3. Each point will be discussed in turn below.

13.2. Objective 1: To test the variability of the ultrasonic echo-tracking equipment in the measurement of AAA wall diameter and distensibility

Intra- and inter-observer CVME for directly measured variables (Dmax and BP) were low ($\leq 10\%$) while CVME for the derived variables (Ep and β) were higher (21-35%). The measured variables were all skewed. However, there is no non-parametric equivalent of the CVME. A logarithmic transformation was applied to the data on β before the CVME was calculated and the resultant CVME's were 10.2% and 8.6% for observers A and B respectively. This suggested that the high level of variation was in fact due to the large variation of Ep and β within the study population rather than due to the technique itself (Wilson et al 2000). Variability of the Diamove technique was deemed clinically acceptable.

The following selection criteria were devised to minimise variability and were used throughout the larger study:-

- 1) The maximum diameter measurements should be within 5% of the estimated value, or 2mm if the aneurysm is less than 4 cm wide.
- 2) At least three consecutive cardiac cycles producing uniform waves should be selected for analysis.
- 3) Patients with arrhythmias should be excluded.

13.3. Objective 2: To test the effect of using brachial pressure as opposed to derived central pressure in distensibility measurement

One year into the study the technology to assess central blood pressure non-invasively using pulse wave analysis (PWA) became available. The peripheral pressure waveform was recorded and transformed into the corresponding central waveform using an integral transfer function. This generated derived central diastolic and systolic pressures, which could be used in the calculation of E_p and β .

Distensibility calculated using brachial and central pressures could therefore be compared.

The principle finding of the study was that use of brachial pressure as opposed to central aortic pressure significantly increased E_p by 13% and β by 12%. However, it was concluded that the systematic nature and the small size of the overestimate rendered brachial pressure acceptable clinically. There remains a debate amongst authors regarding the validity of applanation tonometry in central BP measurement and so brachial sphygmomanometry continued to be used in this study.

13.4. Objective 3: To describe the range of values of aortic wall distensibility using E_p and β in a population with AAA of $\geq 3.0\text{cm}$ anteroposterior diameter

13.4.1 Follow-up of the study population

216 subjects were recruited of whom 210 (97%) produced usable data. Of those who produced usable data, 54% were followed for 12 months and 36% of subjects were followed for more than 18 months.

Follow-up ended because of rupture or repair of the AAA, illness preventing attendance or death. Significantly more AAA ruptured in females (23%) than in males (10%). Significantly fewer females than males were operated on electively. However, in this population the outcome of surgical repair was not significantly different between the sexes. Whether rupture occurred more often in females because of differing AAA structure or simply because fewer were operated remains unclear.

13.4.2. Baseline descriptive statistics

The narrow IQR of diameter (41-54mm), diastolic pressure (72-90 mmHg) and systolic pressure (130-160 mmHg) suggested that the group was relatively homogenous in terms of these variables. However, there was large diversity in wall distensibility among AAA of the same diameter. This may explain, at least in part, why AAA behaviour can be so difficult to predict. At baseline, distensibility was inversely related to diameter but there was no clear pattern of relationship between distensibility and blood pressure, except that β was less pressure dependent than E_p .

13.4.3 Outcome events

Baseline age and AAA diameter were greater in the rupture group than in the intact AAA group, but distensibility did not differ according to outcome. Although AAA in females were more likely to rupture than in males, there were no statistical differences in age, blood pressure and diameter between gender groups. The relationships between the variables were different in each gender, suggesting that female AAA wall degradation may have occurred at a different rate than in male AAA. The AAA which ruptured, or were more likely to rupture (female AAA), tended toward being more distensible and exhibited different dynamic relationships between diameter and distensibility compared with AAA which were intact at the end of the study. It may be that AAA wall degeneration in females is more advanced than in males with AAA of a similar diameter.

13.4.4 Last follow-up

At present it is not known whether the changes in AAA wall structure and composition leading to rupture occur within days, weeks or months of the event. In view of the time interval between baseline data collection and the outcome of interest [median 19.7 (IQR) (9.2-29.9) months], the descriptive statistics at the last follow-up before outcome were analysed next. The time between last follow-up and the outcome of interest was, on average, 3 months.

E_p and β were no longer correlated with diameter in spite of being correlated at baseline. This suggests that the changes in D_{max} and distensibility became divergent during AAA progression. It also suggests that the absolute value of E_p and β were

perhaps not as indicative of rupture risk as the relationship between diameter and distensibility.

When looking at these data with respect to gender, it was apparent that the change in the relationships between diameter and distensibility had taken place in the males. There had been a correlation between diameter and distensibility in the male study population at baseline and but this was no longer the case at last follow-up. The reason for the lack of correlation between diameter and distensibility in females was not immediately obvious. However, in view of the change in relationships between Dmax and distensibility in males at the time of last follow-up, the likely explanation was that there was a difference in the structural integrity of the more advanced AAA, which was not necessarily dependent on diameter.

As with the baseline data, the correlations between variables at last follow-up differed between the sexes but there were no differences between absolute values for each of the variables between the genders. It would appear from this finding, and the knowledge that females had a higher risk of AAA rupture, that similar combinations of diameter, blood pressure and distensibility have more serious consequences for females than males. The female AAA would appear to be unable to withstand the same dynamic combination of pressure, diameter, pressure change and resultant diameter change as the male AAA and therefore may benefit from a different interventional protocol.

Diastolic pressure may play an important part in the events leading up to rupture. This was suggested by the finding that diastolic pressure remained significantly higher in

the rupture group compared with the intact AAA group while systolic, PP and MAP were not significantly different.

13.5. Objective 4: To describe the natural history of AAA wall distensibility, as measured by E_p and β

The rate of change of diameter, distensibility and blood pressure prior to rupture is unknown and may vary considerably between different aneurysms. In the rupture group, the median (IQR) time difference between last data collection and the rupture was 102 (60- 270) days, which may have been too long to 'catch' the changes in AAA wall distensibility and diameter leading to imminent rupture.

Nevertheless, univariate analyses were carried out on the change in variables between the penultimate and the last follow-up. Aneurysms which ruptured did not show significantly different rates of change in diameter or distensibility per month when compared to AAA that remained intact. Neither did females, who have been shown to have a higher relative risk of AAA rupture, show significantly different rates of change in diameter or distensibility per month when compared to males. When change in diameter was correlated with change in distensibility there were no significant correlations. Again, it was apparent that diameter and distensibility did not change at the same rate nor did distensibility change in a consistent direction.

The lack of any significant difference in expansion rates between the rupture and the non-rupture group suggests that either there was no difference between the rupture and intact groups, or (perhaps more likely) that the time interval between last follow-up and rupture was indeed too long to include the vital changes. Although change in

diameter and distensibility were calculated per unit of time (month), the data could not show whether the rate of change was consistent throughout the follow-up interval. If the rate of change in diameter and distensibility altered only during the very last part of the last follow-up to rupture period, this altered rate of change would have been diluted by the slower overall rate of change over the total last follow-up to rupture interval.

The analysis could have been left at this inconclusive point, but it was felt that some attempt should be made to predict the possible changes in diameter and distensibility at the time of rupture. The next stage of the analysis addressed this challenge.

13.6. Objective 5. To test the hypothesis that AAA wall distensibility is related to risk of rupture, and to describe this relationship

13.6.1 The models used in the multiple regression analyses

The Cox proportional hazard model was used to investigate the relationships between distensibility and rupture adjusting for all the other variables collected (diameter, blood pressure, smoking, co-morbidity, drug use, family history). Relative change in diameter and distensibility were included in this analysis to investigate whether they were related to rupture risk or, more specifically, to investigate whether relative change in these variables was more relevant to rupture risk than absolute change. The Cox proportional hazard model was carried out on two sets of variables with time to rupture as the dependent variable. Stepwise regression was used to assess the influence of each variable on time to rupture, thus producing models A and B. Model

C used the same variables as model B but used the 'best fit' regression method to assess the influence of each variable on time to rupture.

13.6.2. The findings of models A, B and C

Model A examined the effect of blood pressure, maximum diameter (and its change), E_p (and its change) and β (and its change) on time to rupture. There was a significantly increased risk of rupture associated with female gender, larger maximum diameter and higher diastolic blood pressure, and a decreased rupture risk associated with increased proportional change in E_p . The decreased relative hazard for change in E_p meant that a larger reduction in E_p (relative to the previous follow-up) was related to a shorter time to rupture.

This model was adjusted for age and sex but did not take co-morbidity, smoking and drug history into account. It gave a simplified picture of the interactions between blood pressure, diameter and distensibility in AAA. This analysis was deemed important as it provided an assessment of the impact of the haemodynamic variables, which could easily be collected at routine follow-up clinics, on rupture risk. It showed that if no other information is collected, gender, diastolic blood pressure, diameter and changing E_p can provide a more accurate risk assessment than diameter alone. It also suggests that absolute E_p is not as indicative of rupture as the relative change in E_p over time.

Model B examined the effect of blood pressure, D_{max} , E_p and β (and their change), hypertension, smoking, beta-blocker use, claudication, angina, family history, MI and CABG on time to rupture. Patients who smoked fewer cigarettes had a shorter time to

rupture but this finding was possibly due to confounding; females smoked fewer cigarettes but had a higher risk of rupture. In addition, self-reported smoking status is known to be inaccurate. Plasma cotinine levels would have provided a more accurate assessment of smoking status, but could not be collected in this study.

In spite of beta-blocker use, the presence of hypertension and previous history of angina, MI and claudication, being entered into the model none of these had a significant influence on time until rupture. Diastolic BP was significantly related to time until rupture whereas the presence of hypertension was not.

Model C assessed the same variables as model B but used the 'goodness of fit' regression method. This included the non-significant variables in each model and gave their significance levels, unlike stepwise regression used in model B which composed the final model from only the most significant variable at each step. It was thought that model B may have used such a rigorous method of final variable selection that variables with a bearing on rupture risk were excluded. The 'best fit' method, producing model C, was thought to have produced a broader picture of factors impacting on rupture risk.

The final model C was the best 6-variable model, which included age, sex, diameter, change in E_p , change in β and smoking. These findings were similar to those of model A in that female gender, higher AAA diameter and a decrease in E_p were related to a shorter time to rupture.

Although diastolic BP did not feature in model C, it can be seen from Table 11.4 that it was included in the 8-variable model. Determining which model to use as the final model was an arbitrary choice. It was based on the balance between creating an over-complex model, which is difficult to interpret, and omitting variables that impact upon rupture risk. The conclusions drawn from the final model C regarding diastolic BP and rupture risk should not be that diastolic BP was not relevant to rupture risk assessment, but that it was not as strong a predictor of time to rupture as the variables which were included.

The findings of models A and C suggest that Ep does play a statistically significant part in predicting time until rupture. It is possible that increasing Ep and diameter, followed by a period of Ep reduction alongside a continued increase in diameter, may indicate an increased likelihood of rupture.

The high variability of distensibility cannot be easily explained nor overlooked. There was no clear pattern of underlying distensibility that could be matched to AAA expansion. There are several factors that may have caused variation in distensibility. The immediate effect of cigarette smoking on aortic distensibility is not yet understood. Cigarette smoking in the minutes before distensibility measurement was not accounted for nor avoided. Likewise, the timing of beta-blocker ingestion and the effect of a transient, anxiety-induced increase in blood pressure could not be accounted for but may have temporarily affected aortic distensibility. These points do not detract from the information provided by distensibility but they do limit the clinical applicability of the findings.

13.7. Objective 6: To assess whether smoking, concomitant vascular disease or medication influence aneurysm size, growth or distensibility

13.7.1 Angina and claudication

Atheromatous plaque within the AAA wall may lead to altered wall mechanics and consequently altered response to pressure and diameter change. However, since atheromatous plaque occurs in such a high proportion of AAA it may not provide any distinctive change in behaviour indicative of rupture. In this study, angina and claudication were used as indicators of atherosclerosis to assess whether this disease process would affect AAA distensibility or risk of rupture. The presence of angina or claudication did not affect wall distensibility, nor were these subjects different with respect to age, aortic diameter or risk of rupture.

13.7.2 Smoking

In this study population, those who had never smoked were significantly older than the smokers, but diameter, E_p and β were not different between these groups. There were no significant differences in diameter, E_p or β between the groups divided into tertiles of pack-years. This finding could not be attributed to heavy smokers dying of other diseases as there were no significant differences in the number of deaths in each tertile group of pack-years smoked ($p=0.46$), nor were there any significant differences in numbers of ruptures in each group ($p=0.32$).

Although this finding suggests that those who smoked least had a shorter time until rupture it may have been confounded by three factors:

- Females smoked less than males and were more likely to rupture (RR 2.24).

- Older subjects smoked less, but were more likely to rupture (RR 2.65).
- Self reported smoking status is known to be inaccurate and invariably results in the underestimation of smoking habit.

13.7.3 Hypertension

Hypertension has been shown to be related to increased AAA expansion and rupture (Englund *et al* 1998, Vardulaki *et al* 2000), with diastolic pressure perhaps being a more accurate predictor than systolic pressure. Maximum AAA diameter and Ep were significantly higher in those who were hypertensive at baseline, but β was no different between the two groups. This supports previous reports that hypertension increases expansion (Cronenwett 1996, Englund *et al* 1998) and reduces distensibility (Naydeck *et al* 1999). The RR of rupture in the hypertensive group was twice that of the normotensive subjects (this was significant), this finding is consistent with that of previous work (Cronenwett 1996).

13.7.4 Antihypertensive therapy

Previous studies have suggested that beta-blockers, Ca channel blockers and ACE inhibitors increase aortic distensibility by a combination of blood pressure reduction, smooth muscle relaxation and vasodilation, and reduced vasoconstriction (Savolainen *et al* 1996, Bank 1997, Englund *et al* 1998, Topouchian *et al* 1999).

In this study, those taking antihypertensive medication were significantly younger than those taking none of the three aforementioned drugs but did not have significantly smaller AAA diameter. This may suggest that the subjects using any of these drugs developed AAA at an earlier age than those not requiring antihypertensive

medication, which in turn, may suggest that a period of untreated hypertension may lead to the formation of AAA at an earlier age. However, beta-blocker, ACE inhibitor and Ca channel blocker use did not appear to significantly alter Ep or β . Although these data do not clearly support previous findings (Savolainen *et al* 1996, Bank 1997, Englund *et al* 1998, Topouchian *et al* 1999), this may simply reflect the fact that this study was not specifically designed to examine the effect of antihypertensive therapy (circulating levels of β -blockers, ACE inhibitors or Ca channel blockers) on AAA distensibility or rupture.

Chapter 14. Conclusions and future studies

14.1 Conclusions

Ultrasonic echo-tracking technology can reliably measure AAA wall diameter and distensibility and is thus suitable for the purpose of clinical follow-up. Use of brachial pressure systematically overestimates E_p and β . It would be preferable to use intra-aortic pressure but this can not be measured non-invasively at present. The use of pulse wave analysis technology to non-invasively derive central pressure may be a useful surrogate, but its utility is still the subject of much debate in the literature.

Diameter and distensibility appear to be related in the early stages of AAA formation but this relationship becomes weaker as the AAA develops. The rate and direction of change in distensibility is more likely to indicate wall breakdown and rupture risk than absolute distensibility. An increase in distensibility alongside increasing AAA diameter indicates a shorter time to rupture than a decrease in distensibility for the same AAA expansion. However, the change in distensibility indicating imminent rupture may occur so close to the event that it may not be possible to 'catch' this change at 6-month follow-up intervals.

14.2 Future studies

The relationships between distensibility and aneurysm wall matrix degradation require further investigation. It would be useful to measure distensibility immediately prior to surgical repair of an aneurysm, where, simultaneously, a wall sample could be obtained and its structure analysed histologically and biochemically. Unfortunately

this will always be restricted to relatively large or advanced AAA and a comparison cannot be made with small or early AAA.

Advancing our understanding of the final events leading to rupture is essential if an improvement in aneurysm management is to be achieved. Our knowledge is limited at present because the time period during which the final breakdown of collagen (leading to rupture) occurs is not known. It may be different for each aneurysm. A study designed to follow AAA patients on a more frequent basis would shed much light on this process but is perhaps not practicable. The present study achieved an average time lag of 3 months between the last measurement and rupture. It would be exciting to recruit subjects with large or rapidly expanding aneurysms who were willing to attend monthly, for example, and monitor various measures of AAA degeneration including serum and plasma markers, diameter and distensibility.

Appendix I: Questionnaire

The WHO (Rose et al 1977) and Edinburgh Claudication (Leng and Fowkes 1992) questionnaires on angina and claudication were combined with questions on medical, drug and family histories. Clinical data were collected at each follow-up visit in the form of blood pressure measurement, AAA diameter measurement and calculation of change in diameter with each cardiac cycle, pulse and pulse pressure, E_p and β .

One question in the claudication section was missed out in error. Claudication therefore, has been defined as probable, not definite in the analysis without any resultant bias. The question missed out was;

- What do you do if you get the pain when you are still walking?
 1. Stop
 2. Slow down
 3. Continue at same pace

AAA: MEASURES OF WALL COMPLIANCE ASSESSMENT FORM

Study type	
i	ii iii iv

0. Study number □□□□ □□□□

Date

		.			.		
--	--	---	--	--	---	--	--

NHS number

Surgeon □□

1.Surname.....Forename.....

2.Address.....

.....Tel.....

3. Date of Birth . . 4. Age yrs

5. Sex..... M ☐ F ☐

6. Place of Birth.....

7.GP name

8. GP Address.....tel:.....

9. Source of Referral.....

Date of Follow-up 1. . .

2. $\square\square.\square\square.\square\square$

3.

		.			.		
--	--	---	--	--	---	--	--

DOD □□.□□.□□

AAA STUDY: MEASURES OF COMPLIANCE
CONSENT FORM FOR PATIENT OBSERVATION

I (name).....of
(address).....
.....

Hereby consent to being included in a study of aneurysms, the nature and effect
of which have been explained to me by Sister Katie Wilson.

I understand that I have an aortic aneurysm, which is a swelling of my main
blood vessel, the aorta. In order to check the size, compliance and growth of my
aneurysm it will be necessary to carry out an ultrasound examination of my
aorta regularly. This will be carried out every 3-6 months and is pain free and
harmless.

Signed.....Date.....

10. C.O.D.

- 1.....
- 2.....
- 3.....

Patient Info Sheet

GP Sticker

☐

☐

GP Info

Medical Record Sticker

☐

☐

CLINICAL DETAILS

11. Smoking

11.1 Do you smoke

Y ☐

N ☐

If no go to Q11.12

11.2 If yes, cigarettes

Y ☐

N ☐

11.3 pipe

Y ☐

N ☐

11.4 cigars

Y ☐

N ☐

11.5 How many, cigarettes

/day

11.6 oz tobacco

/week

11.7 cigars

/week

11.8 How many years have you smoked throughout your life?

years

11.9 How many cigarettes have you smoked per day throughout that period?

/day

11.10 oz tobacco

/day

11.11 cigars

/week

11.12 Have you ever smoked regularly since you left school?

Y ☐

N ☐

If no, go to Q11.21.

- 11.13 What did you usually smoke ?

cigarettes

Y ☐ N ☐
- 11.14

pipe

Y ☐ N ☐
- 11.15

cigars

Y ☐ N ☐
- 11.16 How many

cigarettes

/day
- 11.17

oz tobacco

/week
- 11.18

cigars

/week
- 11.19 For how many years did you smoke?

. years
- 11.20 How long since you finally gave up smoking?

. years
- 11.21 Is any member of your household a smoker?

Y ☐ N ☐

12 Chest pain

- 12.01 Do you ever get chest pain or discomfort ?

Y ☐ N ☐

If no, go to Q12.08
- 12.02 Do you get this when walking uphill or in a hurry?

Y ☐ N ☐

If no go to Q 12.7
- 12.03 Do you ever get this when you walk at an ordinary pace?

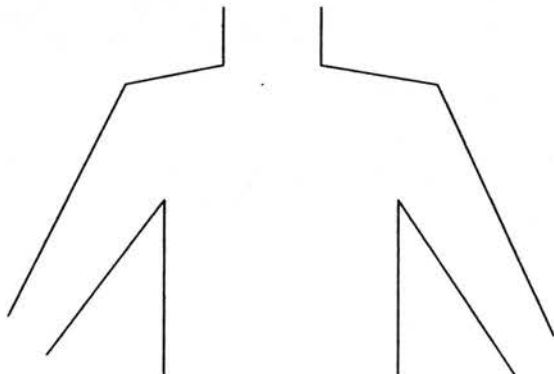
Y ☐ N ☐
- 12.04 When you get any pain what do you do ?

Stop ☐ Slow down ☐ Continue at same pace ☐
- 12.05 Does it go away when standing still or sitting down?

Y ☐ N ☐
- 12.06 How soon?

≤ 10 mins ☐ ≥ 10 mins ☐
- 12.07 Where do you get this pain or discomfort ?

Mark place with an X



12.08 Have you ever had severe chest pain across the front of your chest lasting for half an hour or longer?

Y ☐ N ☐

12.09 What was the cause?

Unknown ☐

Angina ☐

MI ☐

12.10 Has patient ever had coronary artery bypass surgery ? Y ☐ N ☐

If yes, year of most recent CABG graft

13. Leg Pain

13.01 Do you get a pain in either leg when walking ? Y ☐ N ☐

13.02 Does this pain ever begin when you are standing still or sitting
Y ☐ N ☐

13.03 Do you ever get pain in your calf or calves ? Y ☐ N ☐

13.04 Do you ever get it when you walk uphill or in a hurry
Y ☐ N ☐

13.05 Do you ever get it when you walk at an ordinary pace on the level
Y ☐ N ☐

13.06 Does this pain ever disappear while you are still walking
Y ☐ N ☐

13.07 What happens if you stand still ?
Usually disappears in 10 mins or less Y ☐ N ☐

13.08 Usually continues for more than 10 mins Y ☐ N ☐

13.09 Have you ever had surgery on the arteries of your legs other than for
varicose veins Y ☐ N ☐

13.10 Specify.....

13.11 Have you had surgery to remove toes ? Y ☐ N ☐

13.12 leg below knee Y ☐ N ☐

13.13 leg above knee Y ☐ N ☐

14 Previous medical history

14.01	Has patient ever been treated for hypertension ?	Y	<input type="checkbox"/>	N	<input type="checkbox"/>	
14.02	Diabetes	Y	<input type="checkbox"/>	N	<input type="checkbox"/>	
14.03	If yes to diabetes	Diet	Y	<input type="checkbox"/>	N	<input type="checkbox"/>
14.04	Oral	Y	<input type="checkbox"/>	N	<input type="checkbox"/>	
14.05	Ins	Y	<input type="checkbox"/>	N	<input type="checkbox"/>	
14.06	Hx of major disease.....					
					
					

15	B Blockers	Y	<input type="checkbox"/>	N	<input type="checkbox"/>
	other drugs.....				
				
				

16 Family history

16.1	Father	Y	<input type="checkbox"/>	N	<input type="checkbox"/>
16.2	Mother	Y	<input type="checkbox"/>	N	<input type="checkbox"/>
16.3	Brothers	Y	<input type="checkbox"/>	N	<input type="checkbox"/>
16.4	If yes, number		<input type="checkbox"/>		
16.5	Sisters	Y	<input type="checkbox"/>	N	<input type="checkbox"/>
16.6	If yes, number		<input type="checkbox"/>		

Study Details

Follow-up	0	1	2	3	(Circle)
17	Height		<input type="text"/> <input type="text"/> <input type="text"/> cm		
18	Weight		<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> Kg		
19.1	BP	R	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> mmHg		
19.2		L	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> mmHg		
20	Pulse		<input type="text"/> <input type="text"/> <input type="text"/> bpm		
21	Pulse pressure		<input type="text"/> <input type="text"/> <input type="text"/> mmHg		
22.01	Aortic diameter	min	<input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> mm		
22.02		max	<input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> mm		
22.03		mean	<input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> mm		
23.00	Change in diameter		<input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> mm		
24.00	Press. Strain Elast. Modulus (Ep)		<input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> 10 ⁵ Nm ²		
25.00	Stiffness (β)		<input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> arbitrary units		

Appendix II: Birth and death data, and raw data collected at baseline

Study number	Date of Birth	Gender	Date of Death		Cause of Death	BP (mmHg)		Dmax (mm)	Ep (10 ⁵ Nm ⁻²) (a.u.)	β
			Death	Death		Systolic	Diastolic			
1	16-FEB-1917	M	07-JUN-99		MI	170.00	90.00	48.80	4.04	24.10
2	20-SEP-1917	M	28-MAR-97		PNEUM	198.00	96.00	53.80	3.80	20.20
3	27-APR-1924	M				16.00	70.00	51.10	1.92	15.80
4	04-MAR-1915	M				150.00	100.00	50.60	3.21	19.50
5	27-MAR-1923	M	24-APR-99		Ca	130.00	74.00	39.30	1.31	9.90
6	15-JUL-1924	M				188.00	90.00	98.00	5.09	27.70
7	12-OCT-1927	M				132.00	88.00	44.00	47.60	3.55
8	08-MAY-1915	M	28-JAN-99		RAAA	112.00	70.00	52.80	1.97	16.50
10	19-APR-1929	M				140.00	100.00	44.00	4.66	29.40
11	25-JAN-1926	M				136.00	80.00	56.00	37.80	5.36
12	04-MAY-1918	M	12-MAY-96		PNEUM	192.00	76.00	116.00	50.20	3.03
13	16-SEP-1923	F	17-MAR-98		RAAA	100.00	70.00	30.00	28.80	0.60
16	11-SEP-1930	F				148.00	78.00	70.00	35.00	1.60
17	12-JUN-1933	M				128.00	62.00	66.00	49.90	1.57
18	12-MAY-1925	M				150.00	98.00	52.00	47.80	2.28
19	11-FEB-1925	F				112.00	68.00	44.00	48.40	6.05
20	07-MAR-1923	M				118.00	68.00	50.00	54.70	1.35
21	04-SEP-1918	F	20-JUL-99		CVA	180.00	90.00	90.00	49.30	4.43
22	18-JUL-1922	F	06-APR-96		MI	124.00	74.00	50.00	40.30	2.91
23	20-DEC-1926	M	31-JUL-95		MI	130.00	82.00	48.00	44.80	1.27
24	26-MAY-1919	M	14-JUL-97		PNEUMON	130.00	80.00	50.00	49.50	3.43
25	27-SEP-1933	M				124.00	68.00	56.00	44.30	2.19
26	14-FEB-1934	M	31-OCT-95		MI	122.00	80.00	42.00	29.60	0.84
27	26-FEB-1916	M	28-MAY-97		RAAA	192.00	94.00	98.00	61.20	2.91
28	25-AUG-1920	M				158.00	92.00	66.00	37.80	2.91
29	19-OCT-1929	M				120.00	80.00	40.00	32.80	1.48
30	22-MAR-1921	M				148.00	86.00	62.00	43.00	3.61

Appendix II: Birth and death data, and raw data collected at baseline

Study number	Date of Birth	Gender	Date of Death	Cause of Death	BP (mmHg)		Dmax (mm)	Ep (10 ⁵ Nm ⁻²) (a.u.)	β
					Systolic	Diastolic			
31	28-SEP-1922	M			150.00	80.00	70.00	41.00	2.73
32	05-AUG-1927	F	02-OCT-98	HYPOVOLAE	140.00	70.00	70.00	38.50	3.31
33	02-DEC-1926	F			138.00	60.00	78.00	33.50	2.33
34	18-SEP-1927	M			160.00	80.00	80.00	43.80	2.19
35	22-JUL-1918	M	07-MAY-97	PE	150.00	70.00	80.00	40.60	2.48
36	08-SEP-1929	M			162.00	80.00	82.00	38.60	4.58
37	23-OCT-1922	M			138.00	70.00	68.00	52.70	2.38
38	05-NOV-1918	M			128.00	90.00	38.00	34.20	1.11
39	05-OCT-1920	M			142.00	80.00	62.00	34.50	1.60
40	04-JAN-1921	F			162.00	86.00	76.00	40.10	2.41
41	02-FEB-1932	M			138.00	78.00	60.00	42.60	2.15
42	31-OCT-1930	M			130.00	80.00	50.00	37.60	.55
43	09-AUG-1914	M			130.00	90.00	40.00	48.60	1.70
44	26-MAY-1916	M	02-MAY-96	MI	170.00	100.00	70.00	43.10	1.48
45	02-MAR-1921	F			140.00	80.00	60.00	42.20	2.06
46	13-JAN-1915	M			124.00	70.00	54.00	31.60	1.17
47	24-SEP-1922	F							
49	13-APR-1924	F			134.00	72.00	62.00	33.30	1.56
50	25-DEC-1920	M	22-FEB-96	VF ARRES	150.00	80.00	70.00	43.50	1.56
51	08-FEB-1927	M			110.00	68.00	42.00	34.30	1.63
53	12-APR-1922	M			210.00	80.00	130.00	31.40	2.11
54	31-JUL-1920	M	11-JAN-99	PNEUM	162.00	90.00	72.00	46.40	4.82
55	05-NOV-1917	M	05-DEC-97	RAAA	120.00	70.00	50.00	38.30	1.56
56	23-OCT-1929	F	24-SEP-97	PE	100.00	68.00	32.00	52.40	1.67
57	27-MAY-1925	M			138.00	70.00	68.00	41.20	3.49
58	22-SEP-1931	M			168.00	86.00	82.00	50.40	8.97
59	21-NOV-1924	M			158.00	80.00	78.00	43.60	2.94
61	20-SEP-1923	M			132.00	72.00	60.00	45.00	2.85
62	11-FEB-1920	F			148.00	68.00	80.00	41.40	1.91
63	24-MAY-1920	M	19-OCT-97	MI	144.00	66.00	78.00	40.00	3.94
65	29-MAR-1920	F	18-JUN-99	RAAA					
66	26-OCT-1911	M	30-JAN-97	MI	124.00	80.00	44.00	73.90	2.39
									17.90

Appendix II: Birth and death data, and raw data collected at baseline

Study number	Date of Birth	Gender	Date of Death	Cause of Death	BP (mmHg)		Dmax (mm)	Ep (10 ⁵ Nm ⁻²) (a.u.)	β
					Systolic	Diastolic			
67	10-MAY-1922	M			122.00	68.00	54.00	49.80	2.10
68	10-OCT-1923	F	6-OCT-99	RAAA	150.00	86.00	64.00	43.90	2.85
69	25-DEC-1919	M			2.00	76.00	56.00	42.50	2.29
70	02-APR-1920	M	5-APR-97	RAAA	116.00	78.00	38.00	77.20	4.54
71	06-MAR-1929	M							
72	23-JAN-1917	M			30.00	80.00	50.00	48.50	1.95
73	31-OCT-1929	M			62.00	84.00	78.00	30.80	4.30
74	25-MAR-1928	M			124.00	80.00	44.00	47.10	5.77
75	15-OCT-1915	M	6-NOV-95	RAAA	140.00	90.00	50.00	58.90	3.50
76	27-OCT-1926	M			38.00	80.00	58.00	39.60	4.70
77	25-NOV-1930	F	3-MAR-99	RAAA	72.00	70.00	102.00	49.20	2.79
78	26-JAN-1918	M	3-MAY-96	MI	124.00	80.00	44.00	50.00	2.61
79	30-JAN-1916	M			64.00	68.00	96.00	52.90	3.64
80	07-MAR-1924	M			110.00	90.00	20.00	53.10	1.01
81	10-APR-1918	F	2-OCT-96	VF ARREST	174.00	122.00	52.00	55.40	2.06
82	31-DEC-1917	M			18.00	70.00	48.00	55.80	1.22
83	08-JUL-1920	M			18.00	72.00	46.00	54.20	3.42
84	13-JUN-1925	M			78.00	82.00	96.00	33.30	9.46
85	04-MAR-1920	M	08-NOV-96	PNEUM	138.00	100.00	38.00	53.10	1.58
86	30-APR-1917	M	7-APR-96	RAAA	158.00	88.00	70.00	51.30	3.72
87	12-NOV-1924	M			02.00	88.00	114.00	56.60	4.22
88	30-MAY-1924	M	08-MAR-96	RAAA	152.00	92.00	60.00	73.70	2.42
89	03-JUN-1920	F	9-SEP-95	RAAA	148.00	96.00	52.00	79.20	1.59
90	24-MAR-1928	M	22-SEP-95	RAAA	150.00	104.00	46.00	41.70	2.26
91	01-MAR-1926	M			138.00	70.00	68.00	52.70	5.29
92	03-AUG-1925	M	1-APR-97	RESP FAIL	140.00	100.00	40.00	67.50	5.98
93	18-DEC-1911	F	9-JUL-97	RAAA	132.00	82.00	50.00	54.90	1.40
94	24-DEC-1918	F			48.00	84.00	64.00	47.30	2.37
95	07-MAY-1916	F	05-JUN-96	RAAA	158.00	86.00	72.00	64.70	2.37
96	26-OCT-1919	M	-JAN-97	NEUM	138.00	92.00	46.00	42.70	1.71
97	18-DEC-1925	M			12.00	62.00	50.00	36.00	1.86
98	04-AUG-1918	M	5-MAY-96	RAAA					

pendix II: Birth and death data, and raw data collected at baseline

Study number	Date of Birth	Gender	Date of Death	Cause of Death	BP (mmHg)		Dmax (mm)	Ep (10 ⁵ Nm ⁻²) (a.u.)	β
					Systolic	Diastolic			
99	05-AUG-1916.	M			116.00	60.00	56.00	51.30	1.97
100	22-APR-1921	M	19-MAR-99	MI	150.00	80.00	70.00	61.30	2.82
101	25-JUN-1922	M	30-JAN-99	PNEUM	124.00	74.00	50.00	54.90	5.10
102	22-APR-1927.	M			124.00	74.00	50.00	50.20	9.23
103	01-JUN-1926	F	21-DEC-97	MI	150.00	80.00	70.00	58.40	8.51
104	20-JUL-1918.	F			150.00	74.00	76.00	42.00	2.98
105	21-JAN-1914	M	17-FEB-98	RAAA	140.00	90.00	50.00	53.20	4.56
106	02-DEC-1919	F	17-AUG-97	RAAA	150.00	110.00	40.00	54.50	1.66
107	05-FEB-1919.	M			142.00	70.00	72.00	49.50	3.72
108	17-JUL-1922.	F			150.00	92.00	58.00	70.30	1.93
109	26-JAN-1914	M	04-DEC-97	CA (abdo)	138.00	78.00	60.00	49.70	2.54
110	20-OCT-1916.	M			180.00	82.00	98.00	49.80	4.76
111	27-MAY-1916	M			120.00	72.00	48.00	55.50	1.68
112	20-MAY-1944	M			140.00	100.00	40.00	50.60	4.07
113	19-APR-1930.	M			140.00	90.00	50.00	53.20	2.68
114	02-OCT-1926.	M			158.00	78.00	80.00	48.10	7.58
115	27-MAY-1932	M	21-OCT-96	MI	162.00	100.00	62.00	63.70	9.05
116	19-JUN-1915	M	27-JUL-99	MI	24.00	70.00	54.00	51.00	2.28
117	23-SEP-1921	M	14-JUL-97	LVF	60.00	88.00	72.00	51.00	4.99
118	11-JAN-1928.	M			116.00	80.00	36.00	74.00	1.83
119	19-APR-1924.	M			140.00	80.00	60.00	51.40	6.46
120	15-JUL-1913	F	29-SEP-98	CA CERVIX	160.00	90.00	70.00	69.40	2.75
121	26-MAY-1926	M			150.00	78.00	72.00	42.40	3.73
123	04-MAR-1920	M			170.00	100.00	70.00	49.40	2.93
124	16-FEB-1921.	M			150.00	92.00	58.00	58.00	3.12
125	20-JUL-1930.	M							
126	24-OCT-1915.	M			190.00	92.00	98.00	58.50	3.03
127	15-MAR-1915	F			112.00	78.00	34.00	44.10	2.06
128	02-OCT-1920.	F			142.00	82.00	60.00	42.10	2.57
129	10-APR-1925.	F			120.00	102.00	18.00	39.30	.97
130	25-MAY-1931	M	30-JAN-99	CA ABDOM	200.00	90.00	110.00	45.00	8.89
131	11-SEP-1912	F	09-AUG-98	CVA I	40.00	90.00	50.00	53.70	1.50
									10.80

Appendix II: Birth and death data, and raw data collected at baseline

Study number	Date of Birth	Gender	Date of Death	Cause of Death	BP (mmHg)		Dmax (mm)	E _p (10 ⁵ Nm ⁻²)	β
					Systolic	Diastolic			
132	02-APR-1925.	F			150.00	76.00	39.10	5.09	35.10
133	11-APR-1933	M	10-MAR-99	CA LUNG	160.00	82.00			
134	14-JUN-1926.	F			120.00	70.00	41.60	2.18	17.60
135	14-FEB-1914.	M			160.00	80.00	53.00	2.78	18.10
136	10-NOV-1911	M	05-MAY-99	RAAA	118.00	80.00	95.90	3.23	24.80
137	18-JUL-1933.	M			140.00	70.00	47.30	3.41	25.30
138	06-OCT-1927.	M			140.00	76.00	34.40	1.45	10.40
139	11-JAN-1928.	F			132.00	72.00	38.40	4.16	31.50
140	21-JAN-1929	M	15-JUN-98	RAAA	142.00	90.00	46.60	2.06	13.60
141	16-MAR-1919	M			140.00	80.00	58.80	2.05	14.30
142	08-NOV-1931	F	23-AUG-99	CABG	140.00	60.00	40.80	4.35	34.50
143	14-NOV-1928.	M			150.00	98.00	51.20	2.39	14.70
144	23-NOV-1915	M	25-NOV-97	PNEUM	102.00	70.00	53.90	1.99	17.60
145	15-FEB-1932.	F							
146	24-OCT-1915	M	11-JUN-98	CVA	180.00	88.00	46.20	7.11	41.50
147	23-SEP-1918.	M			125.00	64.00	43.20	4.06	33.40
148	15-JUL-1945	M							
149	11-DEC-1923	M			150.00	80.00	42.40	3.66	24.60
150	16-MAR-1914	M			180.00	106.00	74.00	6.81	36.60
151	11-APR-1926.	F			160.00	80.00	40.30	2.35	15.30
152	13-OCT-1929.	M			150.00	60.00	47.70	2.60	19.80
153	04-DEC-1923.	M			150.00	60.00	38.80	3.34	25.50
154	18-APR-1935.	M			152.00	80.00	41.30	5.32	35.60
155	16-SEP-1928.	M							
156	25-MAR-1922	F			140.00	70.00	39.50	1.70	12.70
157	26-MAY-1921	M							
158	18-MAR-1924	M			134.00	60.00	47.90	2.90	23.60
159	31-DEC-1930.	M							
160	23-JUL-1923.	M			142.00	102.00	55.70	2.74	17.00
161	25-JUL-1933.	F			150.00	72.00	42.90	4.70	33.20
162	09-JAN-1920.	M			110.00	60.00	48.30	3.93	35.70
163	14-DEC-1919	M	13-JAN-00	CVA	145.00	90.00	36.80	1.30	8.50

Appendix II: Birth and death data, and raw data collected at baseline

Study number	Date of Birth	Gender	Date of Death	Cause of Death	BP (mmHg)		Dmax (mm)	Ep (10 ⁵ Nm ⁻²)	β (a.u.)
					Systolic	Diastolic			
164	25-DEC-1937.	M	.	.	148.00	88.00	60.00	40.10	4.25
165	25-NOV-1922.	M	.	.	132.00	76.00	56.00	41.40	3.55
166	09-NOV-1923.	M	.	.	138.00	82.00	56.00	63.60	5.90
167	07-NOV-1912	M	22-AUG-98	RAAA	198.00	104.00	94.00	31.40	6.01
168	29-NOV-1931	M	15-MAR-99	PE	164.00	90.00	74.00	65.00	4.58
169	12-FEB-1920	M	.	.	140.00	86.00	54.00	43.20	1.90
170	05-DEC-1921	F	25-NOV-97	RAAA	128.00	70.00	58.00	39.90	1.77
171	31-MAY-1916	M	31-AUG-98	CA (METS)	140.00	86.00	54.00	60.80	4.37
172	14-JAN-1935.	M	.	.	170.00	90.00	80.00	50.20	9.31
173	13-JAN-1934.	F	.	.	170.00	78.00	92.00	49.10	4.87
174	20-AUG-1919.	M	.	.	110.00	70.00	40.00	47.70	1.94
175	22-SEP-1929.	F	.	.	140.00	90.00	50.00	34.20	2.75
176	18-MAR-1920	F	.	.	152.00	88.00	64.00	43.80	2.34
177	08-MAR-1930	F	29-JUL-99	CA BRONCH	210.00	98.00	112.00	33.70	5.54
178	26-JAN-1920	F	.	.	140.00	102.00	38.00	43.20	.93
180	19-MAY-1931	M
181	19-MAR-1925	F	.	.	154.00	82.00	72.00	40.00	4.80
182	26-FEB-1931.	M	.	.	140.00	80.00	60.00	36.60	1.92
183	17-JUN-1926.	M	.	.	182.00	82.00	100.00	61.20	10.68
184	07-JUN-1927.	M	.	.	122.00	82.00	40.00	47.90	2.92
185	31-JAN-1922.	M	.	.	140.00	80.00	60.00	65.90	2.97
187	29-MAY-1917	F	04-OCT-98	PE	118.00	80.00	38.00	53.60	6.70
188	12-APR-1938	M	11-FEB-99	MULTIPLE	140.00	78.00	62.00	54.60	5.36
190	02-MAY-1922	M	.	.	138.00	78.00	60.00	74.60	3.19
191	25-JAN-1925.	M	.	.	122.00	76.00	46.00	34.40	4.72
192	28-DEC-1938.	M	.	.	112.00	70.00	42.00	36.80	4.27
193	23-OCT-1925.	M	.	.	118.00	80.00	38.00	52.20	1.92
194	28-MAR-1923	M	20-AUG-98	CA	212.00	100.00	112.00	49.00	8.08
195	18-OCT-1930.	F
196	05-JUN-1940.	M	.	.	136.00	90.00	46.00	43.50	2.16
197	02-AUG-1924.	M	.	.	162.00	90.00	72.00	37.60	3.83
198	16-JAN-1920.	M

pendix II: Birth and death data, and raw data collected at baseline

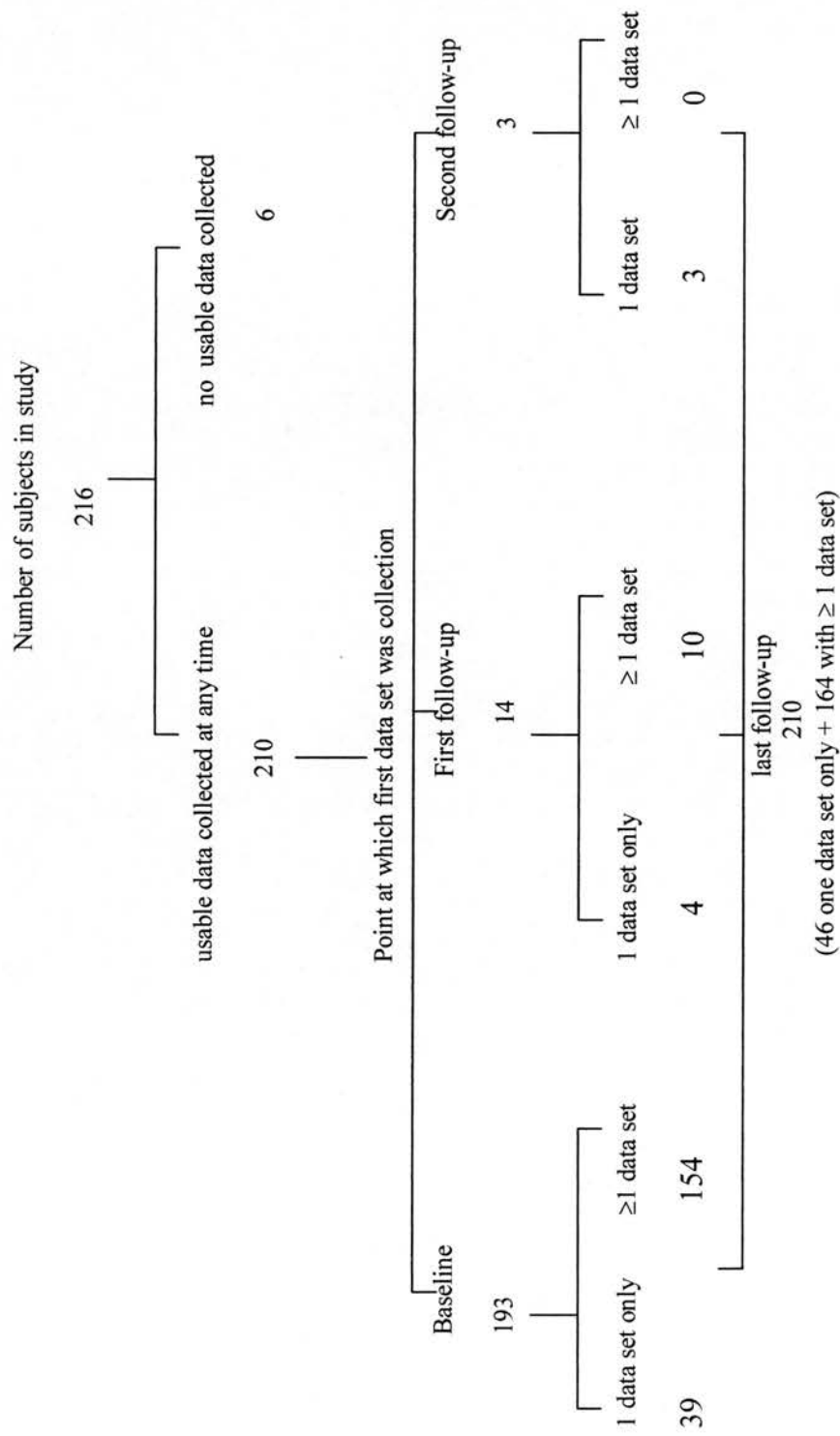
Study number	Date of Birth	Gender	Date of Death	Cause of Death	Systolic	Diastolic	BP (mmHg)	PP (mm)	Dmax (mm)	Ep (10 ⁵ Nm ⁻²)	β (a.u.)
199	03-AUG-1937.	M			112.00	74.00	38.00	46.30	1.73		14.10
200	24-OCT-1921.	M			140.00	70.00	70.00	57.70	2.99		22.20
201	09-AUG-1931.	M			132.00	78.00	54.00	54.20	2.12		15.50
202	22-AUG-1922	F	26-JUL-99	CA (LUNG)
203	13-NOV-1924.	M			170.00	70.00	100.00	47.70	4.21		28.10
204	25-JAN-1928.	F		
205	24-JAN-1910.	M			164.00	80.00	84.00	46.90	4.62		29.60
206	27-JUN-1920.	M		
207	12-MAY-1930	M			120.00	78.00	42.00	38.30	1.85		14.20
208	13-NOV-1919.	M			167.00	92.00	75.00	57.90	2.67		15.90
209	26-SEP-1919.	F			150.00	68.00	82.00	54.20	4.07		29.51
210	07-JAN-1938.	M			152.00	82.00	70.00	57.70	2.93		19.40
211	09-JAN-1921.	M			160.00	80.00	80.00	53.50	4.38		28.40
212	14-AUG-1919.	M			152.00	83.00	69.00	49.30	3.47		22.80
213	26-NOV-1923.	M			172.00	92.00	80.00	55.60	6.68		39.20
214	26-FEB-1920.	M			162.00	82.00	80.00	55.00	4.76		30.40
215	09-JUL-1929.	M			172.00	82.00	90.00	49.30	3.23		19.90
216	15-FEB-1917.	M			115.00	72.00	43.00	50.60	2.58		21.10
217	02-SEP-1923.	M			136.00	73.00	63.00	47.90	4.80		35.50
218	12-MAY-1922	M			128.00	88.00	40.00	102.30	2.52		17.70
219	18-DEC-1910	M	01-AUG-99	RAAA	178.00	90.00	88.00	60.50	4.38		25.40
220	30-NOV-1914.	M			161.00	86.00	75.00	61.40	3.93		24.70
221	03-MAY-1930	M			167.00	109.00	58.00	38.70	5.99		33.00

Appendix IIIa: Number of follow-up visits producing usable data

Baseline	1st follow-up	2nd follow-up	3rd follow-up	4th follow-up	5th-10th follow-up	n
✓	✓	✓	✓	✓	✓	32
✓	✓	✓	✓	-	Y	2
✓	-	✓	✓	✓	✓	2
✓	✓	-	-	✓	✓	1
✓	✓	✓	✓	✓	-	30
✓	-	-	✓	✓	✓	1
✓	✓	✓	✓	-	-	24
✓	✓	✓	-	✓	-	4
✓	✓	-	✓	✓	-	1
✓	-	-	-	✓	✓	1
✓	✓	✓	-	-	-	25
✓	✓	-	✓	-	-	2
✓	✓	-	-	-	-	26
✓	-	✓	-	-	-	2
✓	-	-	✓	-	-	1
✓	-	-	-	-	-	39
-	✓	✓	✓	✓	✓	1
-	✓	✓	✓	✓	-	3
-	✓	✓	✓	-	-	4
-	✓*	✓	-	-	-	2
-	✓*	-	-	-	-	4
-	-	✓*	-	-	-	3
-	-	-	-	-	-	6
et 193	14	3	-	-	-	210

usable distensibility data collected, whether at baseline, first or second visit.

Appendix IIIb: Flow diagram of patients numbers and usable data produced between baseline and last follow-up



Appendix IIIc: Summary of the number of subjects in each stage of analysis

Baseline analysis	193	
Last follow-up analysis	210	
Baseline – last follow-up	154	(193 at baseline – 39 baseline with only 1 data set)
Penultimate –last followup	164*	(210 at last follow-up – 46 who only had 1 data set)

* this number includes one subject on whom only blood pressure data were collected, hence n = 163 in Table 10.2

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Appendix IV: Published work

REVIEW ARTICLE

Expansion Rates of Abdominal Aortic Aneurysm: Current Limitations in Evaluation

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Objectives: Literature on the expansion rate of infrarenal aortic aneurysm is scant. This review was carried out to assess whether there is a normal rate of expansion for infrarenal aortic aneurysms.

Design and methods: Review of literature relating to abdominal aortic aneurysm (AAA) measurement and expansion rates. Articles were identified from a search of the computerised Medline database from 1966 onwards.

Results: Nine studies produced expansion rates for 3.0-5.0 cm AAA ranging from 0.17 to 0.57 cm per year. Evaluation of these studies showed that they are not wholly comparable in terms of source population, sample size, disease definition and period of assessment.

Conclusions: It is not possible to discuss with confidence the "normal" expansion rate of infrarenal aortic aneurysms at any diameter. To elucidate fully the behaviour of AAA, a clear and universal definition of AAA is required in order that it may be used within a large, multicentred prospective cohort study.

Key Words: Aortic aneurysm; Expansion rate; Risk of rupture; Definition.

Introduction

Approximately 900 people per year die from ruptured abdominal aortic aneurysm (AAA) in Scotland.¹ Many of these patients do not survive to reach hospital following rupture but of those who do, 54.7% will die² despite considerable advances made in recent years in surgical and anaesthetic technique, graft materials and postoperative care. The prevalence of AAA is around 5% in patients aged 65 years and increases with age.^{3,4} There would appear to be evidence of a recent rise in prevalence in Western countries; surgical workload is also increasing.⁵⁻⁷ Scottish hospital admissions for AAA rose from 11.5 per 100 000 in 1984 to 33.8 per 100 000 in 1994² and the number of new cases has increased steadily from 283 in 1980 to 612 in 1991.⁸

It is generally held that around two-thirds of patients with untreated AAA die from rupture of the aneurysm,⁹ but this is based on 50-year-old data⁹ and no

reliable natural history data are available. The annual risk of rupture progressively increases with aneurysm size to around 60% if the diameter is greater than 10 cm.¹⁰ Most patients whose aneurysms rupture die without reaching hospital, and virtually all who reach hospital and are not treated within a short time die. In patients who undergo emergency surgery for rupture the 30-day mortality is at best 30%,^{11,12} and more commonly 50%.^{13,14} By contrast, elective surgery for aneurysm carries a mortality of 5% or less^{15,16} depending on the surgeon's selection policies. A reduction in mortality can therefore be achieved by elective surgery in patients at high risk of rupture. Currently the decision to operate on an asymptomatic aneurysm is made chiefly on the basis of diameter, expansion rate and patient fitness.

Aetiology of Aneurysms

Normal aortic wall

The normal aorta is a highly elastic artery with three layers. The innermost layer, the tunica intima, consists

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of a single layer of endothelial cells supported by elastin-rich collagenous tissue. Myointimal cells, which are similar in structure to smooth muscle cells, are scattered throughout the subendothelial tissue. It is here that the accumulation of lipids and intimal thickening of atheroma occurs.¹⁷ The tunica media consists of concentric sheets of elastin, collagen and a small number of smooth muscle cells, and in aneurysmal disease undergoes the most significant changes. The tunica adventitia forms the outer layer of the aorta and consists of collagen with scattered elastin fibres.

The role of collagen and elastin

The collagen and elastin have quite distinct mechanical roles in the aorta. Collagen can only expand by 4% of its original length but provides tensile strength at high pressures preventing over-distension. Elastin can expand by 50–70% of its original length, allowing stress to be distributed uniformly throughout the wall. At low pressures elastin bears most of the stress/pressure load on the aortic wall maintaining the equilibrium between mural haemodynamic stress and the resultant deformation. During aneurysm formation the collagen layer is changed to become densely structured, less pliable and thickened.¹⁷ The result is an arterial wall which has little ability to stretch in response to the cardiac cycle.¹⁸

Normal aortic diameter

The human aorta undergoes expansion throughout life, with a more rapid rate occurring over the age of 60 years.¹⁹ Several authors have suggested that "... ageing plays a far greater role in the widening of the aorta ..." than has previously been acknowledged.^{19–21} Sonesson *et al.*²¹ found that the healthy male aorta expands by 30% between the ages of 25 and 70 years and, perhaps more importantly, the fractional diameter change (aortic wall excursion during the cardiac cycle) at 71 years is 14% of that at 5 years. This can be illustrated by comparing the exponential pressure-diameter curve of a 25-year-old with the more linear curve found in the elderly (Fig. 1). Fractional diameter change is, however, dependent on several physiological variables, namely mean arterial pressure, car-

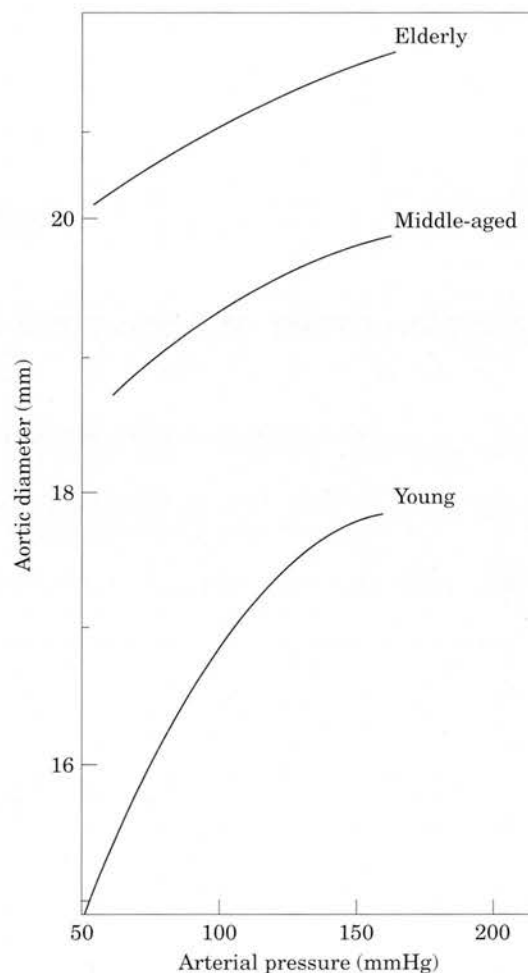


Fig. 1. Pressure-diameter curves of the abdominal aorta compiled from males in the three different age groups; young, middle-aged and elderly. With increasing age the pressure-diameter curves become less steep, the aortic diameter increases and the non-linear behaviour becomes less obvious. Thus, with age the aorta becomes less distensible and dilates. (Reproduced from Sonesson B, Lanne T, Vernerström E, Hansen F. Sex differences in the mechanical properties of the abdominal aorta in human beings. *J Vasc Surg* 1994; 20(6): 959–969).

diac output, stroke volume, heart rate and vessel diameter. This makes it difficult to compare the results of different studies.

Evidence for the effect of ageing on aortic diameter is, however, limited and aortic changes similar to those previously described as aneurysmal growth occur in 12.5–25% of the population with increasing age.²⁰ This implies that the threshold for distinguishing between normal and abnormal aortic diameter is age-dependent.²⁰ It is suggested that at any age level an upper limit for aortic diameter should be chosen which will result in 6% of the population having a diameter greater than the chosen limit, and that this will be sufficiently accurate in the prediction of aneurysm expansion. At this level a 60-year-old male with an

aortic diameter of 24 mm would be followed up, whereas a 75-year-old with aortic diameter of 36 mm would not. These "safe" thresholds are dependent on growth rate, which can be used to dictate intervals between scans.

Aneurysm Formation and Expansion

Aneurysmal formation and expansion occurs in response to the loss of elastin and collagen fibres, which provide resistance to stretching of the wall. Proteolytic activity is due to elastase and collagenase, which are principally produced by macrophages and neutrophil polymorphonuclear cells. These inflammatory infiltrates are often found in AAA walls. However, the respective roles of elastase and collagenase in the formation of aneurysms have not yet been clarified.^{22,23}

The roles of elastolysis, collagenolysis, inflammatory cells and hypertension in the pathogenesis of aneurysms were analysed using two *in vivo* rat models.²² The fragmentation of elastin and attenuation of the media was found to lead to a limited increase in AAA diameter. At this early stage, collagen fibres and intimal/plaque thickening maintain the structural integrity and cylindrical shape of the aorta. The adventitia also appears to increase in circumferential area in order to maintain its original thickness.²³

Subsequently, inflammatory infiltrates, lymphocytes and macrophages cause dissociation of the collagen fibres; the loss of tensile strength leads to the haemodynamic equilibrium becoming unbalanced, with resulting expansion in size of the aorta. Complete rupture is avoided by a complex remodelling process involving neosynthesis of collagen fibres and transformation of the cylindrical aorta to a more spherical aneurysm which compensates for the haemodynamic changes. Plasmin and thioglycollate continue to cause dissociation of the elastin and collagen fibres, leading to progressive dilatation and degeneration of the wall (Fig. 2).^{18,22,23} Hypertension has also been found to be associated with increased inflammation, remodelling and aortic dilatation, and to be a risk factor for AAA expansion.²²

Stereological analysis of volume fractions of the components of aneurysm walls show that collagen and ground substance were increased by up to 77%,^{24,25} whereas the volume fractions of elastin and smooth muscle cells were reduced (elastin by 63–92%^{24,26–28}). Thus, in comparison with normal aortic walls, both the composition, in terms of volume fractions, and the mechanical properties of AAA were significantly altered.²⁵

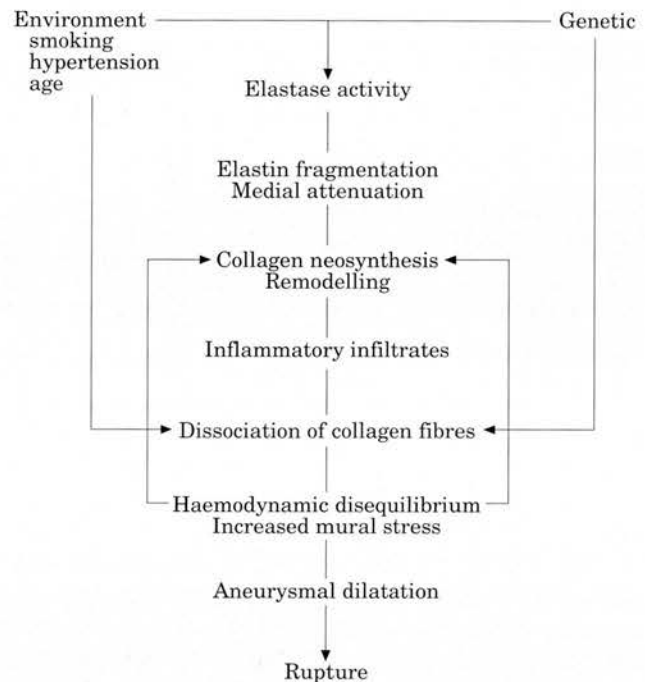


Fig. 2. Pathogenesis of abdominal aortic aneurysm. Modified from McSweeney *et al.*¹⁸

Although atherosclerosis and aneurysm commonly co-exist, the former is thought to be more a pre-disposing factor rather than the single instigator of aneurysm formation. When associated with atherosclerotic occlusion AAA is usually limited to the infrarenal aorta, unlike the variety which is not associated with atherosclerosis when AAA is commonly part of a general arteriomegaly, and therefore multifocal. A comparison of the collagenase activity in patients with and without abdominal aortic aneurysms showed that this enzyme was localised in the aneurysmal wall and was inactive in the vessel wall affected by atherosclerosis. In fact only the aneurysmal walls produced measurable collagenase activity.²⁹

The complexity of the process of aneurysm formation is evident. The precise mechanisms behind the proteolytic activity remain to be clarified, although the overall sequence of events has become more apparent in recent years.

Disease Definition

Several definitions of abdominal aortic aneurysm are used at present, which produces very different results in evaluating the incidence and prevalence of the disease.³⁰ Moher *et al.*³⁰ used three definitions to evaluate disease frequency, case prevalence and prevalence ratio: (1) the Society for Vascular Surgery and the

Table 1. Comparison of estimates of mean annual growth rates at various initial diameter measurements.⁴⁴

Author	No. studied	Growth rate (mm/month)				>6 cm
		3.0–3.9 cm	4.0–4.9 cm	5.0–5.9 cm	Total	
Bernstein <i>et al.</i> ⁴⁶	49	0.26	0.51	—	0.39	
Kremer <i>et al.</i> ³⁸	35	0.19	0.18	—	0.17	
Bernstein and Chan ¹⁶	110	0.39	0.36	0.43	0.37	0.64
Cronenwett <i>et al.</i> ³⁹	67	0.79 (T) 0.19 (AP)	0.45 (T) 0.5 (AP)	—	0.57 (T) 0.22 (AP)	
Delin <i>et al.</i> ³⁷	35	0.54	0.47	0.47	0.52	0.7
Sterpetti <i>et al.</i> ³²	125	0.25	0.4–0.56	—	0.48	
Collin <i>et al.</i> ⁴⁷	50	—	—	—	0.22	
Nevitt <i>et al.</i> ⁴⁵	103	0.26	0.46	—	0.32	
Limet <i>et al.</i> ⁴⁸	114	0.53	0.69	—	—	0.74

International Society of Cardiovascular Surgery (SVS/ISCVS) define an aneurysm as a 50% dilatation of the normal artery adjusted for gender and radiological modality;³¹ (2) Sterpetti *et al.*³² suggest a ratio of infrarenal to suprarenal diameters of ≥ 1.5 ; and (3) Collin³³ defines an abdominal aortic aneurysm as the maximal infrarenal diameter being 4.0 cm or more, or exceeding the maximum diameter of the aorta between the origin of the superior mesenteric and left renal arteries by at least 0.5 cm.

According to the definitions above,³⁰ AAA frequency was found to range from five³³ to 23³² (no units were given). Prevalence rate among the control group was 3.5,³³ or 12.1%,³² and sibling prevalence ratio or relative risk was found to be 0.3³² compared with 1.6³¹ found by the SVS/ISCVS definition.

The latter finding shows most effectively the consequences of differing definitions. Sterpetti's³² study suggests that siblings are at less than half the risk of the normal population of developing an aneurysm, whereas the SVS/ISCVS³¹ data suggest that they are at 1.6 times the risk. The conclusion to be drawn from this comparison of studies is that it is only possible to compare studies with similar definitions, which limits the ability of investigators to pool information from several sources. A definition which is sensitive enough to capture small aneurysms which are likely to become dangerous is essential; however, until a clear and uniform definition is used the true epidemiology of aortic aneurysm will not be elucidated.

Limitations in Assessment of Expansion Rates

Assessment of expansion rate

Aneurysm expansion rates are highly variable, both over time and between different aneurysms.³⁴ It has been well documented that rate of expansion tends to increase exponentially in relation to size at diagnosis.^{34–37} Thus most authors assess growth rates and patterns in subsets of initial diameter (Table 1).

There is considerable variation in the estimates of "normal" expansion rates of AAA within each subset of initial diameter. Small aneurysms (3.0–3.9 cm diameter) have been observed growing at a rate of 0.19–0.79 cm/year,^{38,39} and aneurysms of 4.0–4.9 cm diameter can expand at anything between 0.18 and 0.69 cm/year.^{35,38}

Examination technique

The effect of using differing examination techniques might also have produced a source of incomparability. While some authors suggest that there is no significant difference between radiological modalities, i.e. ultrasound vs. CT scan,³⁰ there are studies that have found that aortic aneurysm size is greater if assessed by ultrasound,⁴⁰ while other studies suggest that CT scanning is the more accurate method of size determination.⁴¹ While the heterogeneity may originate elsewhere, the examination technique employed in the assessment of aortic aneurysm size further complicates meaningful interpretation of the available literature.

Errors in methodology

Many studies based on autopsy findings and referrals are subject to considerable selection bias.^{21,42–44} It may also be the case that the group of patients who are operated on are different from those who rupture or are not considered for surgery, which would compromise the comparability of the groups. The precision of scan measurements is usually ± 5 mm (or within 5%³⁵), in which case a growth rate of 2 mm per year could take 3 years to be recognised, depending on the original size of the aneurysm.²⁰

The large variation in findings among the studies in Table 1 may be due to two quite distinct factors. The authors included in Table 1 may have been comparing

different populations, in which case the rates observed are real and different for each group included. Or, abdominal aortic aneurysms as a group exhibit little or no homogeneity in growth patterns at any stage. In order to investigate this, it is necessary to assess the comparability of these studies, and indeed these authors used a variety of definitions to categorise their subjects.

Selection bias

Within the studies, the populations varied in that some authors included only patients unfit for surgery while others observed all patients. The result is that any effect of the cardiac, respiratory or cerebrovascular conditions preventing surgery have not been evaluated. Aneurysms in patients with co-existing cardio-respiratory disease might have different dynamic characteristics from those with no other serious disease.

Similarly, Limet *et al.*³⁷ used a cohort of all patients admitted to hospital with AAA and observed those unfit for surgery. However, those being admitted to hospital because of a symptomatic or expanding aneurysm may be a different group from those who only require care at an outpatient clinic. A selection process has taken place among these patients which may overestimate the mean expansion rate within the general population of AAA sufferers.

Nevitt *et al.*⁴⁵ claimed that because their population-based study included assessment of ultrasound scans of all patients with AAA, their results were not subject to the same confounding factors as autopsy or admission studies. At specialist referral centres, patients are selected according to severity of disease or symptoms and do not reflect the spectrum of disease in the community.

Sample size

Sample size also has an important influence on the validity of findings. For example, inferences made about the representativeness of the observed characteristics in a sample of the general population are more likely to be correct if the sample size is large. It is not within the remit of this article to assess the optimal sample size for each study reviewed; however, it is important to note the very different sample sizes involved ranging from 35 to 125, further complicating meta-analysis.

Losses to follow-up

Most prospective observational studies suffer losses to follow-up which reduce the validity of the data. Bernstein *et al.*⁴⁶ followed patients for 10 years but gave no indication of the numbers lost in this way nor assessed the effect on their results. The effect of losses to follow-up is dependent on the causes. For example, if patients are lost to follow-up the rate of growth could possibly be an overestimate of "normal" expansion because those with little or no growth may be less motivated to attend outpatient appointments. On the other hand, if patients are lost because they die as a result of aneurysm rupture, estimates of expansion rate may be underestimated.

It would appear, therefore, that in view of the diverse nature of the studies reporting AAA growth rate, most of which are retrospective observation studies, meta-analysis cannot be reliably performed. This is due to the lack of homogeneity in the patients studied, the definitions employed, and the outcomes measured.

Conclusions

The healthy male aorta expands by 30% between the ages of 25 and 70 years and, perhaps more importantly, the fractional diameter change (aortic wall excursion during the cardiac cycle) at 71 years is 14% of that at 5 years. The expected rate of change in aortic diameter is used as an important predictor of the risk of rupture, but the few studies which have assessed expansion rates have produced quite different results.

Evaluation of these studies shows that they are not wholly comparable in terms of source population, sample size, disease definition and period of assessment, thus limiting the value of pooled data. For this reason it is not possible to derive with confidence the expansion rates of aneurysms at any diameter. The possibility remains that abdominal aneurysms, as a group, exhibit little or no homogeneity in growth patterns at any stage. While the SVS/ISCVS definition of an aneurysm as a 50% dilatation of the normal artery adjusted for gender and radiological modality³¹ may be the most realistic definition currently available, it fails to take fully into account the effects of ageing, and until a clear and uniform definition is adopted the true epidemiology and natural history of aortic aneurysm will remain obscure.

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Larger series of patients and longer follow-up have to be gained in order to validate our results and to define preservation characteristics, immunological interactions and clinical use of this conduit.

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Relationship Between Abdominal Aortic Aneurysm Wall Compliance and Clinical Outcome: a Preliminary Analysis

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Background: Aortic compliance, as measured by the pressure-strain elastic modulus (E_p) and stiffness (B), may allow a more precise estimate of abdominal aortic aneurysm rupture risk than size alone.

Aim: To determine the relationships between AAA compliance, size, growth, and clinical outcome.

Methods: One-hundred and twelve patients with initially non-operated AAA (86 men, 26 women, mean age 73 years), recruited from five centres, underwent baseline compliance measurements and were then followed for a median of 7 (range 2-18) months; 85 patients underwent repeated measurements (median 3, range 2-5) 3-6-monthly over a median of 12 (range 3-18 months).

Results: Seven patients have ruptured and 16 have undergone repair of non-ruptured AAA. AAA that ruptured had significantly lower E_p and B (more compliant). In AAA that ruptured or required repair there was an inverse relationship between diameter and E_p and B . In those undergoing repeated measurements AAA expansion was only associated with a significant increase in E_p and B in non-operated patients.

Conclusions: Baseline AAA compliance was significantly related to rupture and the future requirement for operative repair. Failure of compliance to increase with size may be a marker for rapid growth, developmental symptoms and rupture.

Introduction

Ruptured abdominal aortic aneurysm (AAA) is associated with a 30-day combined community and hospital mortality of 90%. By contrast, the mortality associated with elective repair is currently 10% or less in many centres.¹ The decision to operate on an asymptomatic AAA involves weighing the risk of rupture against the risk of operative repair for that individual patient. The risk of rupture is currently estimated primarily on the basis of maximal diameter and growth rate, although both variables are known to be inaccurate predictors of rupture. As no size of AAA appears to be entirely free from the risk of rapid expansion and rupture,² a method which provides a more precise quantification of risk for individual patients is urgently required. It is hypothesised that compliance, which relates directly to aortic wall behaviour and composition, might provide such information. The aim of the present study was to investigate, for the first time, the relationship between

AAA wall compliance, maximum diameter and growth rates in a series of patients, with initially non-operated and asymptomatic AAA.

Patients and Methods

One-hundred and twelve patients with non-operated AAA, recruited from five different centres, underwent baseline compliance measurements, and were followed for a median of 7 (range of 2-18) months. The mean age of the patients was 73 years. There were 86 men and 26 women. Patients were not operated on initially, either because of small size or because of comorbidity which, in the opinion of their surgeon, precluded AAA repair. All patients gave fully informed consent and the study was approved by the local ethics committees. A subset of 85 patients underwent repeated compliance measurements (median 3, range 2-5) at 3-6-monthly intervals over a median follow-up period of 12 (range 3-18) months.

The decision to subsequently operate or not upon a

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patient in this study group was left entirely to the discretion of the consultant surgeons responsible, who were unaware of compliance data. Although it could be argued that stipulating criteria for operation would have allowed the end-points of the study to be defined more precisely, in the opinion of the authors and the relevant ethics committees this would have been unsatisfactory for two reasons. Firstly, at the outset of the study it was not possible to know whether compliance would or would not relate to future aneurysm behaviour. Secondly, any influence exerted by the authors on the decision to operate might have biased the results of the study. The requirement for surgery was precipitated by onset of symptoms (abdominal and/or back pain) in two cases, and in 14 cases because, in the opinion of the responsible consultant, the AAA had enlarged to a point where the benefits of repair outweighed the potential risks.

Compliance was measured by means of an electronic echo-tracking device (Diamove, Teltec, Lund, Sweden) interfaced with a B-mode real-time ultrasound scanner (EUB-240, Hitachi, Tokyo, Japan) fitted with a 3.5 MHz linear array transducer. An echo-tracking phase-locked loop circuit restored the position of an electronic gate relative to the moving echo and yielded the echo movement per unit time. The instrument was equipped with dual echo-tracking which made it possible to track simultaneously two separate echoes from opposing vessel walls. The difference between signals indicated instantaneously the change in vessel diameter. The calculated smallest detectable movement was 7.8 μm , the repetition frequency of the echo-tracking loops was 870 Hz, and the time resolution was therefore approximately 1.2 ms. The data acquisition unit comprised a 486 personal computer (Toshiba) linked to a 12-bit analogue-to-digital converter (Analogue Devices, Norwood, U.S.A.). Change in maximal AAA diameter with cardiac cycle was measured over an 11 s period.

Strain (fractional diameter change) was defined as:

$$\text{Strain} = \frac{\text{maximal systolic diameter} - \text{maximal diastolic diameter}}{\text{maximal diastolic diameter}}$$

The arterial wall distensibility was initially expressed as pressure strain elastic modulus (E_p) where:

$$E_p = K \times \frac{\text{systolic pressure} - \text{diastolic pressure}}{\text{strain}}$$

The constant $K = 133.3$ and allows E_p to be converted from mmHg to Newton (N/m^2).

Because of the non-linear pressure-diameter relationship of the normal arterial wall, E_p is pressure

dependent. Previous workers have observed a linear relation *in vitro* between the logarithm of relative pressure and distension ratio. This index is called stiffness (B) and appears to characterise the entire deformation behaviour of the arterial wall, without pressure dependence, within the physiological range. Stiffness may therefore be a more useful index of aortic compliance than E_p ; although whether this relationship holds true for the human aneurysmal aorta *in vivo* is unknown. The higher E_p and B , the less distensible the artery and the lower the compliance. For a more detailed discussion of these concepts the reader is referred to two recent reviews.^{3,4}

Systolic and diastolic blood pressures were measured in the brachial artery in the usual way by auscultation following inflation and deflation of a sphygmomanometer. Brachial pressure is known to be lower than aortic pressure. However, previous authors^{3,4} have concluded that although E_p and B are consequently under-estimated, this is a systematic error that is likely to affect equally the members of any particular study group. Furthermore, if compliance is to prove a clinically useful variable worthy of routine measurement, its value must be established in relation to brachial pressure rather than a scientifically more robust but impracticable direct intra-arterial measurement of blood pressure. Mean arterial pressure (MAP) was diastolic pressure plus one-third pulse pressure.⁵

Because variables were highly skewed, linear associations between pairs were assessed using Spearman's rank correlation. Data was entered on the Edinburgh University mainframe computer for statistical analysis.

Results

Baseline compliance measurements, size and subsequent outcome

Seven patients have ruptured and 16 have undergone operative repair for non-ruptured AAA; two for symptoms (abdominal and/or back pain) and 14 due to increase in size. Seven patients have died of unrelated causes.

Patients who went on to rupture had a greater baseline maximal AAA diameter than those who were operated for non-rupture, who in turn had larger AAA than those who did not rupture or undergo repair. Patients who ruptured had lower baseline E_p and B than those who were operated for non-rupture, who in turn had lower baseline E_p and B than those who neither ruptured nor were operated (Table 1).

Table 1. Comparison of baseline size, Ep, and B in those patients who went on to rupture, required operative repair of non-ruptured AAA, and those who did not.

Baseline compliance measurements median (range)	Rupture (n=7)	Operated (non-rupture) (n=16)	Not operated or ruptured (n=89)	p value*
Maximal diameter (mm)	54.9 (46.9–72.0)	49.2 (42.4–70.3)	45.0 (28.8–77.2)	$p<0.01$
Strain – Ep (N/m ²)	2.16 (1.59–3.72)	2.45 (1.22–7.58)	2.79 (0.55–9.46)	$p<0.01$
Stiffness – B (arbitrary units)	15 (9.1–23.0)	17.3 (9.9–51.5)	18.2 (4.0–71.6)	$p<0.01$

*Kruskal-Wallis non-parametric ANOVA 3 column comparison of unpaired median values.

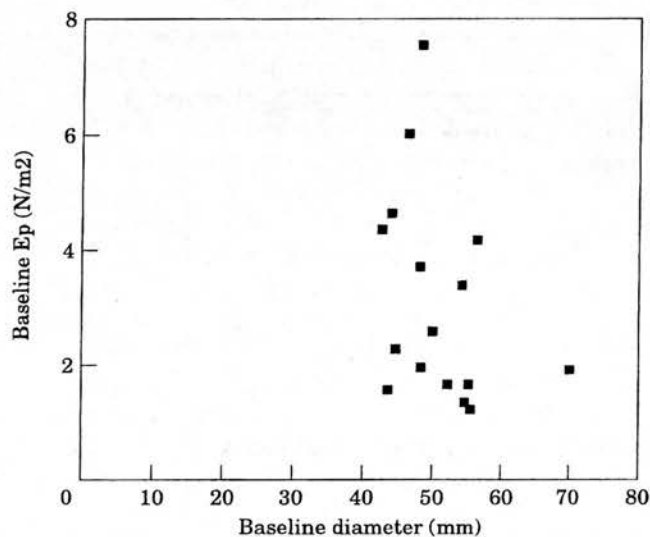


Fig. 1. Correlation between baseline maximal diameter and Ep in patients with non-ruptured AAA that required operative repair; Spearman coefficient, $r = -0.45$, $p = 0.074$.

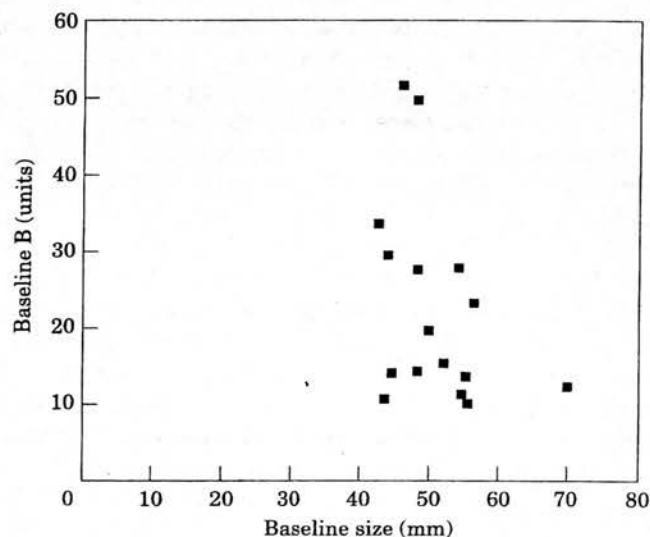


Fig. 2. Correlation between baseline maximal diameter and B in patients with non-ruptured AAA that required operative repair; Spearman coefficient, $r = -0.47$, $p = 0.067$.

Relationship between baseline compliance and size

In patients who subsequently ruptured there was a non-significant inverse relationship between baseline maximal diameter and baseline Ep (Spearman coefficient, $r = -0.25$, $p = 0.6$) and between baseline maximal diameter and baseline B (Spearman coefficient, $r = -0.11$, $p = 0.84$).

Patients who underwent operative repair of non-ruptured AAA also demonstrated a non-significant inverse relationship between baseline maximal diameter and baseline Ep (median 2.45, range 1.22–7.58, N/m²) (Spearman coefficient, $r = -0.45$, $p = 0.074$) (Fig. 1), and between baseline maximal diameter and baseline B (median 17.3, range 9.9–51.5, arbitrary units) ($r = -0.47$, $p = 0.067$) (Fig. 2).

By contrast, in the 89 patients who neither ruptured nor required operative repair ($n = 89$), there was a significant positive correlation between baseline maximal diameter (median 45.0, range 28.8–77.2, mm)

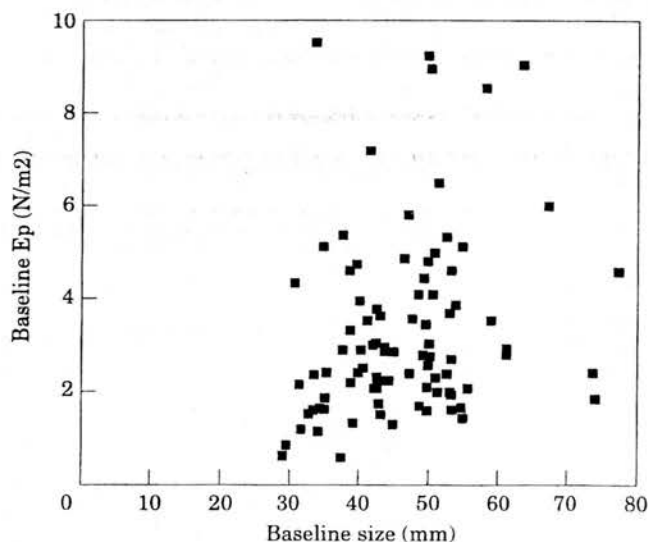


Fig. 3. Relationship between baseline maximal diameter and Ep in patients with AAA which did not rupture or require operative repair; Spearman coefficient, $r = 0.27$, $p < 0.01$.

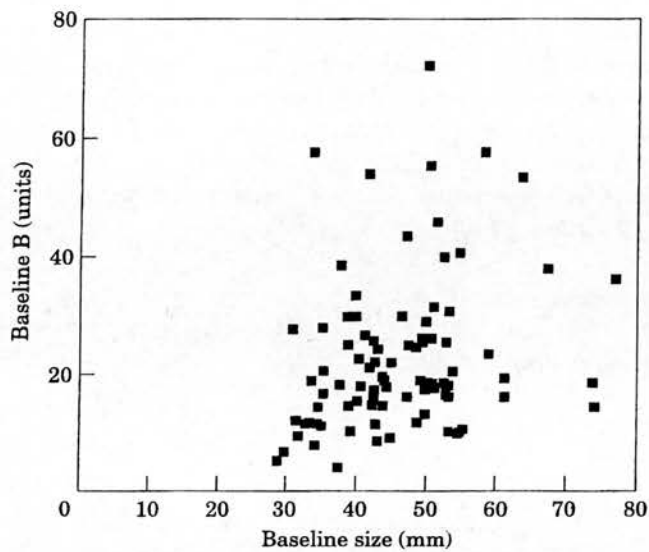


Fig. 4. Relationship between baseline maximal diameter and B in patients with AAA which did not rupture or require operative repair; Spearman coefficient, $r=0.24$, $p=0.018$.

and baseline Ep (median 2.79, range 0.55–9.46, N/m²) (Spearman coefficient, $r=0.27$, $p<0.01$) (Fig. 3); and between baseline maximal diameter- and baseline B (median 18.2, range 4.0–71.6, arbitrary units) ($r=0.24$, $p=0.018$) (Fig. 4).

Change in size and compliance over time

In the subset of 85 patients undergoing repeated compliance measurements, two patients have ruptured, eight have undergone operative repair of non-ruptured AAA and four have died of unrelated causes. Due to small sample size, statistical analysis has been restricted to a comparison of the (non-rupture) operated group and the non-operated groups.

Although there was a significant increase in size in both the operated non-rupture and the non-operated groups over the period of the study, only the non-operated group demonstrated a significant increase in Ep and B; that is, an increase in stiffness (Table 2).

Conclusions

Numerous attempts have been made to predict, on the basis of physical characteristics, which AAA will rupture and which are safe to observe.^{6,7} Previous work has focused upon absolute size (maximal anterior-posterior or transverse diameter, cross-sectional area), relative size (standardised on the basis of patient build, age and sex),⁸ shape (circular vs. elliptical cross-sectional profile on computed tomography),⁹ wall thickness and blistering¹⁰ and expansion rate.^{11,12} Aneurysm size and expansion may, in turn, be affected by other factors such as hypertension¹³ and continued smoking.¹⁴

Unfortunately, the predictive value of these variables, while perhaps being useful in population studies, is insufficient to quantify risk on an individual patient basis. Rupture of small AAA, though uncommon, is well recognised, suggesting that other factors more directly related to aortic wall behaviour may be more important and worthy of study.¹⁵ However, to date, little work has been performed defining the mechanical properties of the aneurysm wall itself.

Aneurysmal dilation of the aorta is associated with a significant decrease in elastin and smooth muscle content and an increase in collagen and ground substance. *In vitro* studies comparing the tensile strength of excised normal and aneurysmal human aorta obtained at surgery or post-mortem have indicated that aneurysmal tissue is much less distensible; and that this loss of compliance is related to loss of elastin from the wall.^{16,17} Aortic compliance, as measured by Doppler ultrasound assessment of pulse wave velocity, is reduced in adults at increased risk of atherosclerosis¹⁸ and such measurements have been proposed as a useful screening test for premature vascular disease.¹⁹

In this prospective study, baseline compliance measurements have been made in order to determine whether differences in compliance might predict rupture and/or the future requirement for operative

Table 2. Comparison of maximal diameter, growth, Ep and B in operated and non-operated patients who underwent repeated compliance measurements.

Operated AAA	Baseline measurement median (range)	Final measurement median (range)	p value*
Maximal diameter (mm)	48.1 (43.5–56.6)	53.1 (46.2–68.6)	$p=0.03$
Strain Ep (N/m ²)	2.85 (1.22–6.05)	3.44 (1.1–6.54)	$p=0.74$
Stiffness B (arbitrary units)	18.6 (9.9–51.5)	20.45 (9.3–45.4)	$p=0.84$
Non-operated AAA	44.3 (28.8–77.2)	49.6 (31.4–80.9)	$p=0.01$
Maximal diameter (mm)			
Strain Ep (N/m ²)	2.42 (0.55–9.23)	3.64 (0.95–8.65)	$p=0.0038$
Stiffness B (arbitrary units)	18.1 (4.0–71.6)	25.2 (7.5–60.3)	$p=0.002$

* Wilcoxon signed rank test for paired, non-parametric data.

intervention on account of symptoms or expansion. Both compliance and maximal diameter varied widely in the rupture, the non-rupture operated, and the non-rupture non-operated groups. The principal finding is that AAA which subsequently ruptured or required operative repair, while being significantly larger at baseline, possessed significantly lower Ep and B. In other words, size for size, AAA which rupture or require elective repair appear to be more compliant than those AAA that do not.

The fundamental question is, therefore, whether such compliance data can be used independently of diameter to predict which AAA are at risk of rupture. In this respect, interesting relationships between compliance and size in the different clinical groups were observed. The relationship between compliance and size in the non-operated, non-ruptured group was similar to that found in a previous retrospective study of 60 patients with non-operated, non-ruptured AAA.²⁰ In these patients, as their AAA increases in size there is a significant increase in both Ep and B; that is, the aneurysm becomes stiffer and less compliant as it grows. By contrast, in patients who subsequently rupture or require operative intervention, Ep and B fail to increase or even fall as the AAA grows.

It is possible that a single baseline compliance measurement might be misleading if both size and compliance were to change between that time and the time the AAA ruptures or is repaired. For this reason, repeated measurements were performed in a subset of patients to determine whether a change in compliance over time might relate to future clinical outcomes. The principal finding is that the relationship between compliance and size observed in the clinical groups is also observed in individual AAAs over time. Thus, while there was a significant increase in size in both operated and non-operated AAA, only the non-operated AAAs demonstrated a significant increase in Ep and B. In the operated AAA, increasing size was not associated with a significant increase in stiffness.

Taken together, these preliminary data suggest that, while a single baseline compliance measurement may be able to distinguish those AAA that subsequently rupture or require operative repair, changes in compliance over time are likely to be a better predictor of future behaviour. In particular, failure of compliance to decrease with size, and/or an increase in the compliance of a large AAA over time, may be markers for above average growth, onset of symptoms, and rupture.

One might speculate that small AAA are more compliant than large AAA because they retain many of the features of the normal arterial wall in that a significant

proportion of the wall still comprises elastin. As AAA enlarge, elastin is replaced with collagen and compliance decreases; that is, they become stiffer. Once AAA reach a certain size, which may vary considerably between different patients, it may be possible to differentiate AAA on the basis of compliance measurements into two types:

(a) *Type I AAA*. Further enlargement is accompanied by further increases in stiffness. This increase in stiffness is due to increasing collagen deposition and/or remodelling in the aortic wall which actually confers strength to the AAA such that the risk of rupture is, in fact, low.

(b) *Type II AAA*. Further enlargement is not associated with an increase in stiffness and, in fact, stiffness may even fall. This may be because of a failure to lay down and remodel collagen, leading to the production of an aortic wall which is weak or "thinning". It is these AAA that may be at risk of rupture.

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We should like to thank all the surgeons who have contributed their patients to this and other ongoing studies of AAA compliance: Mr McCollum, Mr Stonebridge (Ninewells Hospital, Dundee); Ms Howd, Mr Turner (Queen Margaret Hospital, Dunfermline); Mr Cooper, Mr Engeset (Aberdeen Royal Infirmary); Mr Duncan (Raigmore Hospital, Inverness); Mr McKay (Gartnavel Hospital, Glasgow); Mr Chamberlain, Mr Jones, Mr Wyatt, Mr Lees, Mr Lambert (Freeman Hospital, Newcastle); Mr McCormick, Mr Muir (Dumfries and Galloway Royal Infirmary); Mr Jenkins, Mr Murie, Professor Ruckley, Mr Bradbury (Edinburgh Royal Infirmary). This project was funded by the British Heart Foundation.

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A 10-year Follow-up of Patients Presenting with Ischaemic Rest Pain of the Lower Limbs

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Objectives: To determine the 10-year outcome of patients presenting with rest pain.

Methods: One hundred and three consecutive patients presenting with ischaemic rest pain in 1987 were followed up after 10 years. Hospital notes, death certificates and telephone interviews with patients were used to determine outcome.

Results: Follow-up data is available for 97 (94%) patients. Thirteen patients are alive (13.7%) after 10 years, 12 presented with rest pain alone and one had ulceration. Three of these had amputation. The commonest cause of death was myocardial infarction ($n=21$, 25%). In those who had died, the median age of onset of symptoms was 72 years (49-93) for rest pain, 74 years (56-87) for ulceration and 71.5 years (45-85) for gangrene. Their survival after admission was a mean of 39 months with rest pain, 33 months with ulceration and 42 months with gangrene. The overall 5-year survival was 31% and the 10-year survival 13%.

Conclusion: Patients presenting with ischaemic rest pain have a poor prognosis. The presence or absence of ulceration or gangrene does not influence the outcome. Most patients die from smoking-related diseases.

Key Words: Critical limb ischaemia; Risk factors; Survival.

Introduction

Patients presenting with symptomatic peripheral vascular disease have widespread arterial disease. In patients with intermittent claudication, 50-60% will have an improvement in their symptoms following changes in lifestyle, e.g. cessation of smoking and commencement of regular exercise.^{1,2} However, 34-45% of these patients are dead within 6 years due to ischaemic heart disease.³ The prognosis in patients presenting with rest pain is worse. They are often elderly and frail and despite aggressive management their long-term survival may be poor. In 1987, a study on a cohort of 103 patients with rest pain presenting to this hospital and reported by Berridge *et al.*⁴ showed that this group of patients often have multi-system disease with multiple risk factors. This is now a long-term follow-up of the same group of patients with the aim of assessing survival, factors that affect survival and causes of death.

Methods

Design

A retrospective review of the outcome in patients with rest pain at a minimum follow-up of 10 years.

Patients

One-hundred and three consecutive patients admitted to hospital in 1987 for treatment of lower limb ischaemic rest pain. This included patients with rest pain alone, those with rest and ulceration, and those with rest pain and gangrene. Patients with a history of previous vascular reconstruction within the preceding 6 months were excluded. Ten years later data was available on 97 of these 103 patients (94%).

Data collection

Data on risk factors including age, sex, diabetes, hypertension, renal failure, ischaemic heart disease, admission haemoglobin concentration, white cell count

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A prospective randomized multicentre comparison of expanded polytetrafluoroethylene and gelatin-sealed knitted Dacron grafts for femoropopliteal bypass

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Purpose: To compare graft patency between expanded polytetrafluoroethylene (PTFE) and gelatin-sealed knitted Dacron for femoropopliteal bypass. **Methods:** A prospective, multicentre trial was performed in 108 patients randomized to receive either a PTFE or Dacron prosthetic graft. Distal anastomosis was above knee in 75 and below knee in 33 patients. **Results:** Primary patency at 1, 2 and 3 years was 72, 52 and 52% for PTFE, and 70, 56 and 47% for Dacron ($P = 0.87$). Secondary patency at 1, 2 and 3 years was 74, 54 and 54% for PTFE and 78, 70 and 53% for Dacron ($P = 0.39$). The most significant predictors of early graft failure were poor vessel run-off ($P = 0.04$) and critical limb ischaemia ($P = 0.04$). **Conclusion:** There was no difference in graft patency between PTFE and Dacron for femoropopliteal bypass. © 1999 The International Society for Cardiovascular Surgery. Published by Elsevier Science Ltd. All rights reserved.

Keywords: Dacron, femoropopliteal bypass, polytetrafluoroethylene

It is generally accepted that autologous saphenous vein is the first choice for femoropopliteal bypass grafting although some consider polytetrafluoroethylene (PTFE) grafts equally acceptable or even preferable for primary above-knee arterial reconstruction [1, 2]. Choice of the most suitable synthetic prosthetic graft for femoropopliteal reconstruction remains controversial. Retrospective studies comparing PTFE with knitted Dacron at 5 years with respect to graft patency have varied from similar patency rates [3] to superiority of Dacron over PTFE [4].

The aim of this study was to compare graft patency between PTFE and gelatin-sealed knitted Dacron graft by a prospective, randomized trial.

Methods

The study was approved by the institutional ethics committees of the participating hospitals. Patients requiring a femoropopliteal bypass for disabling claudication or critical limb ischaemia, and who had absent or unusable saphenous vein, were considered eligible for entry into the study. Between October 1991 and November 1995, 108 consecutive patients receiving a prosthetic graft for femoropopliteal bypass were recruited into the trial. Patients were randomized at each of the participating centres to receive either a PTFE or a Dacron graft (Gelsoft, Vascutek, UK).

Demographic and risk factors assessed were age, sex, ischaemic heart disease, hypertension, diabetes, smoking, indication for surgery (disabling claudication or critical limb ischaemia comprising rest pain, ulceration or gangrene), previous vascular procedure involving the same extremity, arteriographic

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there is considerable heterogeneity with respect to compliance. There was no relationship between growth rate and E_p or β .

In summary, therefore, the present study has confirmed that abdominal aortic aneurysm are significantly less compliant than the normal aorta, that compliance is inversely related to size, and that among abdominal aortic aneurysm of similar size compliance varies 10-fold. Compliance does not, however, appear to be related to growth rate. Taken together these data suggest that if aortic wall compliance is related to rupture, and because the authors are currently conducting a prospective study to determine whether this is the case, then this predictive information would largely be independent of, and so additional to, that currently derived from size and growth rate alone.

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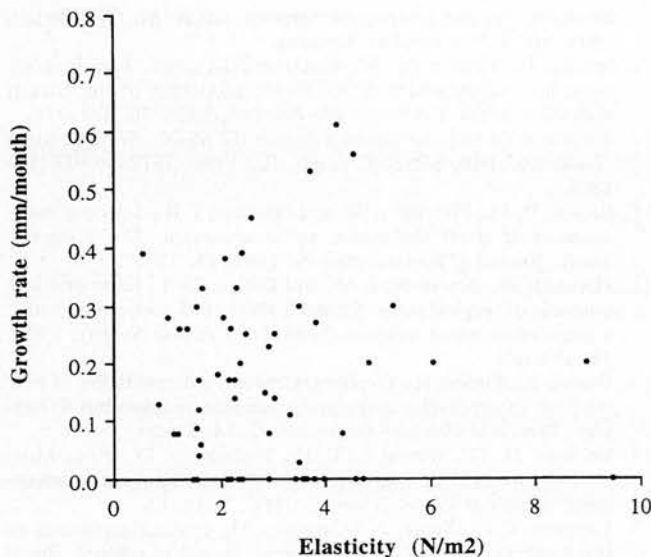


Figure 3 Scatter plot showing the relationship between growth rate and elastic modulus (Ep): $r = -0.09$, $P = 0.25$ Spearman's rank correlation

that this loss of compliance is related to loss of elastin from the wall [21, 22]. Aortic compliance, as measured by Doppler ultrasound assessment of pulse wave velocity, is reduced in adults at increased risk of atherosclerosis [23] and such measurements have been proposed as a useful screening test for premature vascular disease [24].

The echo-tracking system used in the current study has been used previously to define the mechanical properties of the normal human aorta. In young (20- to 30-year-old) healthy subjects the compliance of the normal distal aorta in man has been estimated to be $Ep = 0.7 \text{ N/m}^2$ (\pm s.d. 0.25) and $\beta = 5.97$ (\pm s.d. 1.45) units [25]. As part of the normal ageing process aortic diameter increases and compliance decreases, such that by the seventh decade of life $Ep = 3.37 \text{ N/m}^2$ (\pm s.d. 1.01) and $\beta = 23.50$ units (\pm s.d. 7.57) [25]. Although both Ep and β increase exponentially with age, the increase is less in female subjects, and the large standard deviations in the above data indicate that there is considerable variability between individuals [26, 27]. There also appear to be marked differences between different arteries in the same individual. For example, the decrease in carotid compliance with age is significantly less than that found in the aorta [28]. These workers also determined compliance in 37 patients with abdominal aortic aneurysm in whom the mean maximal diameter was 41.6 mm (\pm s.d. 14), the Ep 5.04 N/m^2 (\pm s.d. 2.53) and $\beta = 34.87$ units (\pm s.d. 24.46). Abdominal aortic aneurysms were significantly less compliant than normal sized aortas from an age-matched population in terms of Ep but not β . The individual variation in compliance appeared to be even greater in the aneurysmal than

in the normal aorta population but no significant correlation was found between abdominal aortic aneurysm diameter and either Ep or β , and growth rate was not measured. The present study has obtained similar values for Ep and β in abdominal aortic aneurysm, and has demonstrated for the first time that in a series of non-operated, non-ruptured abdominal aortic aneurysm, there is an inverse relationship between maximal diameter and compliance.

A study using M-mode echocardiography to measure aortic distensibility in 30 patients with abdominal aortic aneurysm also found that aneurysmal dilatation was associated with decreased compliance [29]. These authors reported a median Ep of 31.2 N/cm^2 , and commented on the wide variation in compliance between different abdominal aortic aneurysm. However, unlike the current larger study, they did not report a significant relationship between Ep and aortic diameter, and they did not calculate stiffness (β). In a histological study of 15 operated patients they found a significant inverse correlation between compliance and elastin content of the aortic wall.

The present study indicates that larger abdominal aortic aneurysm tend to grow more quickly, although abdominal aortic aneurysm of similar size showed considerable heterogeneity in this respect. This has been observed by some [30] but not all [31] previous workers. In general, the growth rates observed in the current study, median 0.16 mm per month or 1.9 mm per year, are low in comparison with previous data: probably because patients exhibiting rapid expansion had been operated on.

There was a highly significant positive correlation between Ep and β . Although both terms are expressions of compliance, Ep is said to be pressure dependent and β not so. This is confirmed by the significant correlation between mean arterial pressure and Ep , but not between mean arterial pressure and β . However, it must be remembered that these expressions were derived from data that relate to normal arteries and the same may not be true of aneurysmal tissue. In normal arteries, compliance decreases as the wall is distended by increasing pressure. In abdominal aortic aneurysm, compliance varies less with mean arterial pressure, as abdominal aortic aneurysm may be stiff throughout the physiological pressure range. This is suggested by previous work that indicated that Ep is related to mean arterial pressure in normal subjects but not in patients with abdominal aortic aneurysm [29]. Both large size and rapid expansion are thought to be associated with an increased risk of rupture. There was a significant positive correlation between Ep and size, and also a tendency for larger aneurysms to exhibit greater stiffness; although the strength of these relationships indicates that within a population

Table 1 Spearman's rank correlation coefficients and significance values describing the relationship between maximum aortic diameter*, mean arterial pressure, growth rate, elastic modulus and stiffness

	Max. aortic diameter* (mm)	Mean arterial pressure (mmHg)	Elastic modulus (Ep) (N/m ²)	Stiffness (β) (arbitrary units)
Growth rate (mm/month)	$r = 0.59$ $P < 0.001$	$r = 0.04$ $P < 0.77$	$r = -0.09$ $P = 0.25$	$r = -0.13$ $P = 0.15$
Stiffness (β) (arbitrary units)	$r = 0.16$ $P = 0.11$	$r = -0.08$ $P < 0.61$	$r = 0.96$ $P < 0.001$	
Elasticity (Ep) (N/m ²)	$r = 0.22$ $P < 0.05$	$r = -0.31$ $P < 0.031$		
Mean arterial pressure (mm/Hg)	$r = 0.15$ $P = 0.13$			

*At the time of compliance measurement.

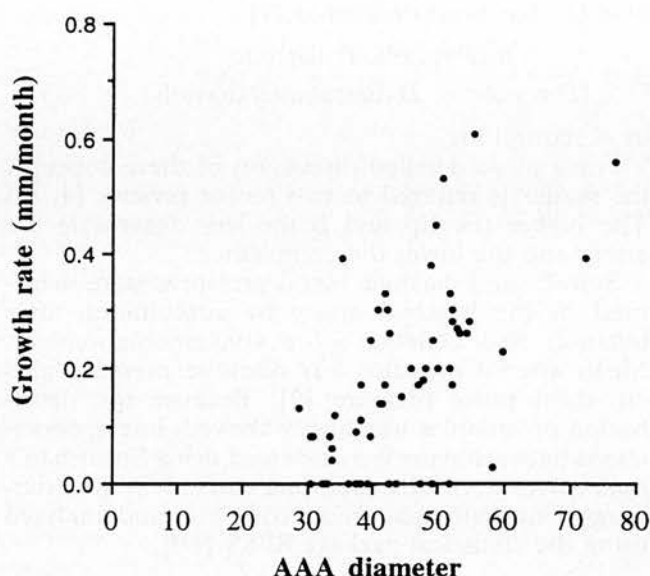


Figure 1 Scatter plot of the relationship between abdominal aortic aneurysm diameter and growth rate; $r = 0.59$, $P < 0.001$, Spearman's rank correlation

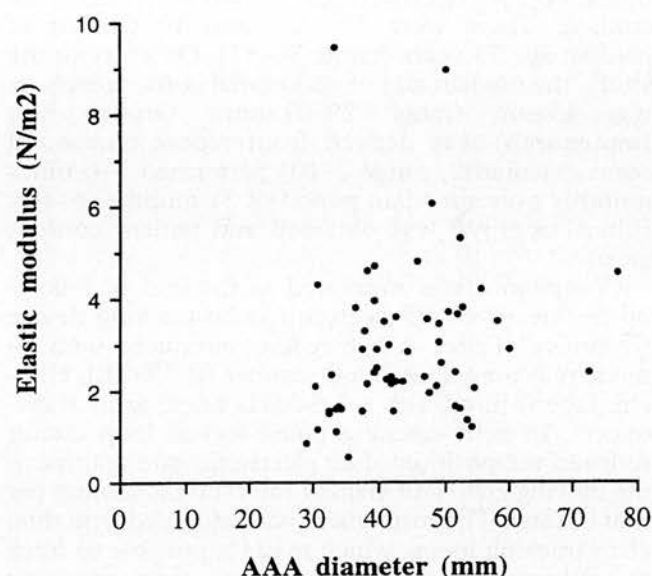


Figure 2 Scatter plot showing the relationship between abdominal aortic aneurysm diameter and elastic modulus (Ep); $r = 0.22$, $P < 0.05$; Spearman's rank correlation

of similar size showed a 10-fold variation with regard to both Ep and β . There was no significant relationship between growth rate and Ep, (Figure 3) or between growth rate and β .

Discussion

Numerous attempts have been made to predict, on the basis of physical characteristics, which abdominal aortic aneurysm will rupture and which are safe to observe [11, 12]. Previous work has focused upon absolute size (maximal antero-posterior or transverse diameter or cross-sectional area), relative size (standardized on the basis of patient build, age and sex) [13], shape (circular *versus* elliptical cross-sectional profile on computed tomography) [14], wall thickness and blistering [15], and expansion rate [16,

17]. Aneurysm size and expansion may in turn be affected by patient factors, such as hypertension [18] and continued smoking [19].

Unfortunately, the predictive value of these parameters, while perhaps relevant to population studies, are insufficiently accurate to quantify risk on an individual patient basis. Rupture of small abdominal aortic aneurysm, though less common, is well recognized, which suggests that other factors more directly related to aortic wall behaviour may be more important and worthy of study [20]. However, to date, little work has been performed defining the mechanical properties of the aneurysm wall itself.

In vitro studies that compared tensile strength of excised normal and aneurysmal human aorta obtained at surgery or post mortem have indicated that aneurysmal tissue is much less distensible, and

quantification of risk is required. It is possible that compliance, which relates to aortic wall composition and behaviour, might provide further information. The aim of the present study was to investigate, for the first time, the relationship between abdominal aortic aneurysm wall compliance, maximum diameter and growth rate in a series of patients with non-operated, asymptomatic abdominal aortic aneurysm.

Methods

Sixty patients were recruited from five separate vascular surgical centres in Scotland with asymptomatic abdominal aortic aneurysm that were not operated on due to small size, low growth rate, unacceptable operative risk, advanced age or patient wishes were studied. There were 50 men and 10 women of median age 73 years (range 56–81). On entry to the study, the median size of abdominal aortic aneurysm was 43 mm (range 29–67 mm). Growth rate (mm/month) was derived from repeat ultrasound scans (median 2, range 2–10) performed 3–6 times monthly over a median period of 21 months (6–48). Ethical approval was obtained and patient consent given.

Compliance was measured at the end of follow-up by means of an electronic echo-tracking device (Diamove, Teltec AB, Sweden) interfaced with B-mode real-time ultrasound scanner (EUB-240, Hitachi, Japan) fitted with a 3.5-MHz linear array transducer. An echo-tracking phase-locked loop circuit restored the position of an electronic gate relative to the moving echo and yielded the echo movement per unit of time. The instrument was equipped with dual echo-tracking loops, which made it possible to track two separate echoes simultaneously from opposing walls. The difference between signals indicated, instantaneously, the change in vessel diameter. The smallest detectable movement was 7.8 μm , the repetition frequency of the echo-tracking loops was 870 Hz, and the time resolution was therefore approximately 1.2 ms. The data acquisition unit comprised a 486 personal computer (Toshiba) linked to a 12-bit analogue to digital converter (Analogue Devices, Norwood, USA). Change in maximal abdominal aortic aneurysm diameter with cardiac cycle was measured over an 11-second period. Strain (fractional diameter change) was defined as:

Strain =

$$\frac{\text{maximal systolic diameter} - \text{maximal diastolic diameter}}{\text{maximal diastolic diameter}}$$

The arterial wall distensibility was initially expressed as pressure strain elastic modulus (E_p) [6] where:

$$E_p = K \times \frac{\text{systolic pressure} - \text{diastolic pressure}}{\text{strain}}$$

The constant $K = 133.3$ allows E_p to be converted from mmHg to N/m^2 .

Because of the non-linear relationship of the normal arterial wall, E_p is pressure dependent. Previous workers have observed a linear relation *in vitro* between the logarithm of systolic/diastolic pressure ratio. This index is called stiffness (β) and appears to characterize the entire deformation behaviour of the arterial wall, without pressure dependence and within the physiological range. Stiffness may then be a more useful index of aortic compliance than E_p ; although whether this relationship holds true for the human aneurysmal aorta *in vivo* is unknown. Stiffness (β) has been defined as [7]

$$\beta = \frac{\ln(P_{\text{systolic}}/P_{\text{diastolic}})}{(D_{\text{systolic}} - D_{\text{diastolic}})/D_{\text{diastolic}}}$$

\ln = natural log

For a more detailed discussion of these concepts the reader is referred to two recent reviews [4, 8]. The higher the E_p and β the less distensible the artery and the lower the compliance

Systolic and diastolic blood pressures were measured in the brachial artery by auscultation after inflation and deflation of a sphygmomanometer. Mean arterial pressure was diastolic pressure plus one-third pulse pressure [9]. Because the distribution of variables was highly skewed, linear associations between pairs were assessed using Spearman's rank correlation. The data were entered on the Edinburgh University mainframe computer and analysed using the statistical package SPSS [10].

Results

At the time of compliance measurements, median (range) diastolic pressure was 80 mmHg (60–122 mmHg); systolic pressure was 139 mmHg (100–210 mmHg); pulse pressure was 61 mmHg (20–130); and mean arterial pressure was 98 mmHg (79–139). Abdominal aortic aneurysm size, E_p , β and growth rate did not differ between male and female patients.

Table 1 shows that there was a significant positive correlation between mean arterial pressure and E_p , and between E_p and β , but not between mean arterial pressure and β . There was a significant positive correlation between growth rate (median 0.16 mm/month, range 0.0–0.61) and maximal aortic diameter (median 43 mm, range 29–77) (Figure 1). There was a significant positive correlation between maximum diameter and E_p (median E_p 2.42 N/m^2 , range 0.55–9.46) (Figure 2), but not between maximum diameter and β (median 17.7 units, range 4.0–57.3). Abdominal aortic aneurysm

The relationship between abdominal aortic aneurysm wall compliance, maximum diameter and growth rate

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Aim: Aortic compliance as measured by the pressure–strain elastic modulus (Ep) and stiffness (β), may allow a more precise estimate of rupture risk. The aim of this study was to determine the relationships between compliance, maximal aneurysm diameter and growth rate. **Methods:** Sixty abdominal aortic aneurysm patients of median age 73 years, were studied. Growth rate was derived from repeat ultrasound scans obtained over a median period of 21 months (range 6–48). At the end of follow-up, patients underwent measurement of maximum aortic diameter, Ep and β using the Diamove echo-tracking system. **Results:** Growth rate correlated positively ($r = 0.6$, $P < 0.01$) with maximum diameter on entry to the study. There was a positive correlation between mean arterial pressure and Ep ($r = 0.3$, $P = 0.03$), but not between mean arterial pressure and β ($r = 0.8$, $P = 0.61$). A positive correlation was found between final maximum diameter and Ep ($r = 0.22$, $P = 0.04$) but not β ($r = 0.16$, $P = 0.11$). There was no significant relationship between growth rate and Ep or β . **Conclusion:** Large aneurysms tended to be less compliant. Within a population of abdominal aortic aneurysm of similar maximum diameter there was a 10-fold variation in Ep and β . Compliance and growth rate were not related. If aortic compliance is related to risk of rupture then this predictive information is likely to be largely independent of that currently obtained from size and growth rate. © 1999 The International Society for Cardiovascular Surgery. Published by Elsevier Science Ltd. All rights reserved.

Keywords: abdominal aortic aneurysm, compliance, rupture risk

Introduction

Ruptured abdominal aortic aneurysm is associated with a 30-day combined community and hospital mortality of 90% [1]. By contrast, the mortality associated with elective repair is reported to be less than 5% in a number of centres [2, 3]. Following success-

ful repair of abdominal aortic aneurysm, patients may return to a near normal life expectancy [4]. The decision to operate on an asymptomatic abdominal aortic aneurysm involves weighing the risk of rupture against the risk of operative repair for the individual patient. The risk of rupture is estimated primarily on the basis of maximum diameter and growth rate, although both parameters are known to be inaccurate predictors of rupture. As no size of abdominal aortic aneurysm appears to be entirely free of risk of rapid expansion and rupture [5] on an individual patient basis, a method that provides a more precise

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Ultrasonic measurement of abdominal aortic aneurysm wall compliance: A reproducibility study

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Purpose: The purpose of this study was to examine the intraobserver and interobserver error associated with ultrasonic echo-tracking compliance measurement in patients with abdominal aortic aneurysm.

Methods: Two observers independently measured brachial blood pressure by sphygmomanometer and maximum aortic diameter, pressure strain elastic modulus (Ep) and stiffness using an ultrasonic echo-tracker. The observer was blind to several variables: pulse pressure, diameter change, Ep, and stiffness. In study 1, observer A measured compliance in 13 patients at 30 to 60 minutes apart. In study 2, observers A and B each measured compliance on 23 patients at two visits, 2 weeks apart.

Results: There were no significant differences within observer A's compliance measurements. The coefficients of variation of method error (CV_{ME}) for directly measured variables were systolic blood pressure, 7.3%; diastolic blood pressure, 5.4%; and maximum aortic diameter, 2.6%. CV_{ME} values for derived variables were Ep, 21.2%, and stiffness, 17.6%. No differences were found between observers A and B and visits 1 and 2. CV_{ME} values were 7.9% or less for directly measured variables and 32.7% or less for derived variables. These CV_{ME} values were greatly reduced when the calculation was made with the use of log transformed data.

Conclusion: The high CV_{ME} value for derived variables is largely due to their wide variation within this population. This technique can measure abdominal aortic aneurysm diameter and compliance with an acceptable level of intraobserver and interobserver error. (J Vasc Surg 2000;31:507-13.)

The decision to operate on a patient with an asymptomatic abdominal aortic aneurysm (AAA) involves weighing the risks of rupture against those of operative repair. Although cohort studies indicate that rupture is related to maximum AAA diameter (Dmax),

growth rate, and blood pressure (BP), none of these variables reliably predicts the behavior of individual aneurysms.¹ Because no size of AAA is entirely free from risk of rupture, a variable that provides a more precise quantification of risk is required. Previous work has suggested that AAA wall compliance (expressed as elastic strain modulus [Ep] and stiffness and measured by means of a commercially available ultrasound echo-tracking system [Diamove; Teltec AB, Sweden]) may be related to future growth rate and risk of rupture.²

Compliance is a measure of the relationship between stress (force per unit area of wall) and strain (fractional deformation of wall). In the context of the normal arterial wall, compliance is most accurately described by the change in volume of a segment of artery in relation to pulsatile change in BP.³ However, measurement of changes in wall thickness in response to changes in pressure and vessel volume are necessary to calculate true vessel compliance.⁴ At present, neither variable can be reliably measured in the aorta in vivo. Arterial wall distensibility (which describes the relationship between relative diameter

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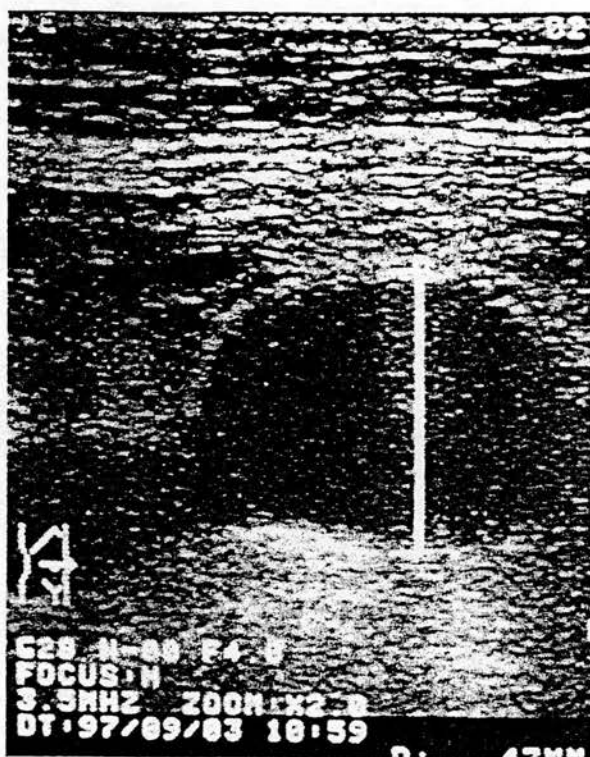


Fig 1. Longitudinal view of AAA with the cursor tracking the anterior and posterior walls.

change and pressure) has been used by a number of researchers⁴⁻⁶ as a surrogate measure of compliance.

Peterson et al³ introduced the equation $Ep = K (P_{\text{systolic}} - P_{\text{diastolic}}) / ([D_{\text{systolic}} - D_{\text{diastolic}}] / D_{\text{diastolic}})$, where $K = 133.3$, P = pressure, and D = aortic diameter. Ep is a measure of the structural distensibility of the artery, rather than a measure of the elasticity of the arterial wall material.⁴

Hayashi⁷ proposed the term *stiffness* (β) to describe the viscoelastic behavior of arteries within the physiologic pressure range: $\beta = \ln(P_{\text{systolic}} / P_{\text{diastolic}}) / ([D_{\text{systolic}} - D_{\text{diastolic}}] / D_{\text{diastolic}})$. Both Ep and stiffness are inversely related to distensibility and compliance. These concepts are discussed more fully in two recent reviews.^{8,9}

Measurement of aortic compliance with the use of an echo-tracking device (Diamove) is reproducible in healthy subjects with no aneurysm.¹⁰ However, this may not be true in patients with AAA because of cardiorespiratory comorbidity, obesity, and variable aneurysm morphologic condition. Preliminary data have suggested a relationship between aortic compliance, future growth, and rupture.² However, before it can be used to aid the selection of patients for

repair, it is essential to quantify the reproducibility of this method. The aim of this study therefore was to examine, for the first time, the intraobserver and interobserver variability associated with a commercial ultrasonic phase-locked echo-tracker in the measurement of AAA compliance with the use of an ultrasound echo-tracking technique.

METHODS

The use of the echo-tracking ultrasound system (Diamove) has been discussed in detail previously.^{8,11-14} A 3.5-MHz linear array transducer was used to provide a standard real-time B-scan image. The transducer was placed over the AAA to obtain a longitudinal section at the point of maximal anteroposterior diameter. The anterior and posterior vessel walls were echo tracked after the initial placement of a cursor within the vessel (Fig 1). During the tracking, the ultrasound pulses were time shared equally between the B-scan image and the A-scan line of interest, allowing the pulsatile changes in vessel diameter to be monitored. A phase-locked loop restored the position of an electronic gate relative to the moving echo; the compensatory movement of the gate yielded the movement of the echo.

Electronic gates were represented on the screen by two cursors. These locked onto the echoes from the posterior lumen/wall interface of the anterior wall and the anterior interface of the posterior wall of the AAA and subsequently measured the D_{max} . The output signal from the echo-tracking circuits represented the distance between the vessel walls. The repetition frequency was 870 Hz, producing a time resolution of 1.15 msec. The calculated smallest detectable movement was 8 μm . Data acquisition and analysis were performed on a Pentium 24X computer (Datalink Computers, Edinburgh, Scotland). The pressure-diameter curve was registered on the computer in real time, and at least three consecutive waves were analyzed. The Diamove software automatically identified the start and end of each cardiac cycle. The operator manually selected the wave forms of interest, and an average wave was produced (Fig 2). Brachial artery pressures were entered, and the derived variables, including Ep and stiffness, were then displayed on the screen. Pulse pressure and diameter change were calculated by Diamove.

BP was measured from the brachial artery in the right arm with a hand-held sphygmomanometer. The right arm was used to prevent bias, based on the assumption that neither arm was more prone to hemodynamically significant vascular disease. The cuff was wrapped around the upper arm and inflated

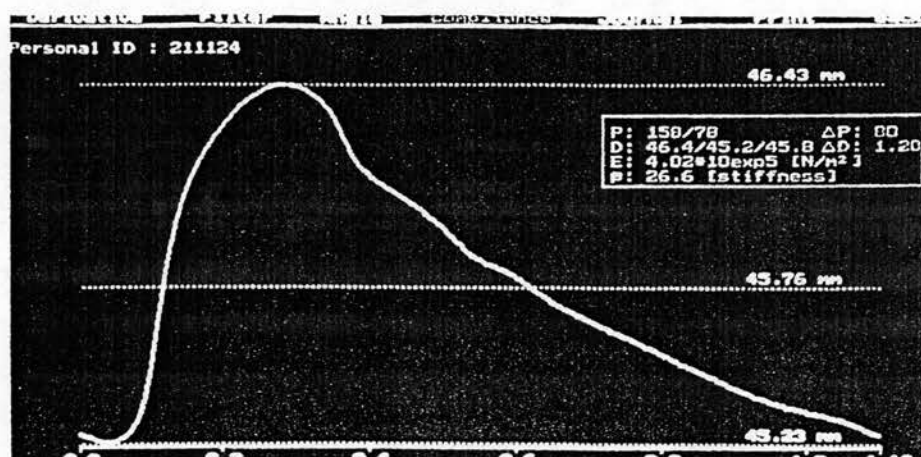


Fig 2. Average wave with calculations of E_p , stiffness, diameter change, systolic and diastolic pressure, and pulse pressure.

until the radial pulse could no longer be felt. The stethoscope was placed over the brachial artery at the antecubital fossa. Systolic pressure was registered as the pressure where the first Korotkoff sounds (phase 1) were heard, although cuff pressure was reduced. Diastolic pressure was registered as the pressure where the final Korotkoff sounds (phase 5) disappeared.¹⁵

Two recordings of diameter change over 4 to 11 seconds were collected on each patient, during each session, with brachial artery pressure measured each time. The best of the two pressure-diameter traces was selected for analysis on the basis of the following criteria: (1) The maximum diameter measurements were within 5% of the estimated value (estimated diameter being taken from a static image of systolic diameter) or 2 mm, if the aneurysm was less than 4 cm wide; (2) at least three consecutive cardiac cycles producing uniform waves were available for analysis; (3) any obvious arrhythmias were excluded; and (4) if all of above were the same, the wave form with the largest diameter and pulsatile diameter change was selected because this was assumed to indicate the point of highest stress:strain ratio.

Observer A underwent 5 months of training in the Departments of Radiology and Vascular Surgery at the University of Edinburgh. Observer B received 2 months of training in the Department of Vascular Surgery at the University of Edinburgh before the study began.

Observers were blind to D_{max} , E_p , and stiffness because these variables were only shown on the

computer screen once analysis had been performed at the end of the study. The observers examined each patient alone and were therefore blind to each other's BP measurements.

Ethics committee approval was given for this study, and informed written consent was obtained from each patient.

Data collection

Study 1. Observer A performed two AAA compliance measurements during two sessions 30 to 60 minutes apart on each of 13 patients during a single visit to the Vascular Studies Unit.

Study 2. Observers A and B performed two AAA compliance measurements on a further 23 patients during each of two visits to the Vascular Studies Unit.

Statistical methods. Data were analyzed with the use of a statistical package (SPSS-X; SPSS, Inc, Chicago, Ill).¹⁶ Medians of the variables in studies 1 and 2 were compared with the Wilcoxon signed rank test to check for systematic bias between the sessions and the observers. The coefficient of variation expresses the SD of a single set of measurements as a percentage of the sample mean. However, in this study, we undertook to express the degree of variability between two sets of measured data. For that reason Bland and Altman's coefficient of variation of method error (CV_{ME})¹⁷ was used. Spearman's rank correlation coefficient¹⁷ was used to assess the linear association of all measurements between and within observers and visits.

Table I. Intraobserver variability in the measurement of AAA wall compliance and brachial artery BP made by observer A at two sessions that were 30 to 60 minutes apart (n = 13 patients)

Variable	Session 1*			Session 2*		
	Median	IQR	Range	Median	IQR	Range
Systolic BP (mm Hg)	140	126-160	122-186	138	123-148	116-184
Diastolic BP (mm Hg)	81	72-83	58-98	77	70-88	58-93
Pulse pressure (mm Hg)	60	56-73	41-108	62	43-67	36-113
Maximum diameter (mm)	51.1	38-56	31-68	50	41-54	31-69
Minimum diameter (mm)	50.3	37-55	29-67	49	39-53	29-68
Diameter change (mm)	1.18	0.82-1.5	0.52-2.38	1.33	0.83-1.59	0.42-2.82
Elasticity (10 ⁵ N/m ²)	3.75	2.2-5.83	1.41-7.07	2.61	1.90-5.49	1.21-8.36
Stiffness	28.08	17.18-40.56	9.85-48.40	21.43	13.5-39.66	8.2-54.25

IQR, Interquartile range.

*Wilcoxon signed rank tests for differences between sessions were all nonsignificant ($P > .05$).

Table II. Median and interquartile range for variables when measured by each observer at each session

Parameters	Visit 1			Visit 2		
	Observer A	Observer B	P value*	Observer A	Observer B	P value*
Systolic BP (mm Hg)	140 (121-157)	138 (126-156)	NS	140 (121-152)	135 (124-152)	NS
Diastolic BP (mm Hg)	76 (68-82)	76 (69-84)	NS	78 (70-81)	78 (72-90)	<.05
Pulse pressure (mm Hg)	61 (46-76)	58 (53-74)	NS	58 (48-76)	54 (49-70)	NS
Maximum diameter (mm)	51.2 (43.3-54.8)	51.9 (44.4-55.4)	<.05	52.3 (45.4-54.5)	51.0 (44.6-56.1)	NS
Diameter change (mm)	1.3 (0.9-2.0)	1.4 (1.0-1.9)	NS	1.0 (0.8-2.2)	1.2 (0.7-2.0)	NS
Elasticity (10 ⁵ N/m ²)	2.8 (2.0-4.5)	3.0 (2.0-4.7)	NS	3.3 (2.5-4.8)	3.5 (2.0-4.6)	NS
Stiffness	19.8 (13.5-29.5)	21.3 (14.2-34.0)	NS	23.1 (16.5-33.9)	24.6 (14.8-33.6)	NS

NS, Not significant.

*Wilcoxon signed rank test of interobserver differences at each visit.

RESULTS

Study 1: Intraobserver variation. Table I shows the median and interquartile range of the variables measured by observer A during sessions 1 and 2. There were no statistically significant differences between the first and second sessions with regard to the distributions of any of the compliance measurements. The intraobserver CV_{ME} values for measurements by observer A were low for the directly measured variables (systolic BP, 7.3%; diastolic BP, 5.4%; and Dmax, 2.6%). The intraobserver CV_{ME} values of the derived variables were higher (Ep, 21.2%, stiffness, 17.6%, and diameter change, 18.2%).

Study 2: Interobserver variability. Table II shows the median and interquartile range of each variable obtained by observers A and B at each visit. Significant interobserver differences were found only with regard to Dmax at visit 1 ($P \leq .05$) and diastolic BP at visit 2 ($P \leq .05$).

All variables reached a high ($r > 0.5$) and significant ($P \leq .05$) degree of intraobserver and interobserver correlation (Table III). Intraobserver and

interobserver measurement of Dmax demonstrated a significant and high degree of correlation ($r \geq 0.96$ and $r \geq 0.94$, respectively). CV_{ME} values for intraobserver and interobserver variation were 10% or less for the variables directly measured by the observers (diastolic BP, systolic BP, and Dmax) and 35% or less for the mathematically derived parameters (Table IV). However, when the values were log transformed before the calculation of the CV_{ME} value, the CV_{ME} value was much reduced. For example, stiffness in Table IV became, for observer A, 10.2%, for observer B, 8.6%, for visit 1, 6.6%, and for visit 2, 10.22%. This is not the correct usage of this test; we have only calculated stiffness to show the effect of skewness on CV_{ME} values.

DISCUSSION

There were no statistically significant differences in intraobserver measurements of any of the compliance variables. Significant interobserver differences were only found in diastolic BP at visit 2 and Dmax at visit 1. Intra- and interobserver CV_{ME} values for

Table III. Median and interquartile range of variables obtained at two sessions by two observers and Spearman's rank correlation coefficients for intraobserver and interobserver measurements of parameters in study 2

Parameters	Median (IQR)	Intraobserver correlation (r)		Interobserver correlation (r)	
		Observer A	Observer B	Visit 1	Visit 2
Systolic BP (mm Hg)	140 (123-153)	0.62*	0.81*	0.85*	0.72*
Diastolic BP (mm Hg)	78 (70-84)	0.81*	0.78*	0.87*	0.82*
Pulse pressure (mm Hg)	58 (50-73)	0.50†	0.83*	0.84*	0.56‡
Maximum diameter (mm)	51.6 (45-55)	0.98*	0.96*	0.95*	0.94*
Diameter change (mm)	1.3 (0.86-2.0)	0.85*	0.77*	0.80*	0.91*
Elasticity (10 ⁵ N/m ²)	3.1 (2.1-4.6)	0.64‡	0.62‡	0.82*	0.66*
Stiffness	22.3 (15.5-32.6)	0.71*	0.68*	0.77*	0.74*

IQR, Interquartile range; P ≤ .001

*P ≤ .001

†P ≤ .05

‡P ≤ .01

Table IV. Coefficients of variation of method error (CV_{ME}) between intraobserver and interobserver measurements of BP, aortic diameter and diameter change, elasticity, and stiffness from study 2

CV _{ME}	Intraobserver (%)		Interobserver (%)	
	Observer A	Observer B	Visit 1	Visit 2
Systolic BP	10.0	8.5	5.1	7.9
Diastolic BP	7.0	7.8	5.7	5.9
Pulse pressure	23.0	13.4	11.9	20.0
Maximum diameter	2.2	3.5	2.2	3.5
Diameter change	18.2	27.0	20.1	18.8
Elasticity (10 ⁵ N/m ²)	35.3	26.0	23.1	32.7
Stiffness	32.0	25.6	21.2	29.4

directly measured variables were low (≤10%), although CV_{ME} values for the derived variables were higher (≤35%).

Variability of the Diamove echo-tracking device has not previously been reported in patients with AAA. However, present data are comparable with those obtained in a previous methodologic study¹⁰ that used healthy subjects with normal aortas (Table V). A third study also investigated aortic compliance in four young (aged, ≤35 years) subjects with no aneurysm¹⁸ and reported on four compliance measurements from each subject during one visit. These authors¹⁸ expressed their methodologic error for Ep and stiffness in terms of SD. SD was not appropriate for the analysis of this group of subjects with AAA because compliance measurements were not normally distributed and were highly variable. The results of Lanne et al¹⁸ are therefore less comparable with the present findings than those of Hansen et al.¹⁰ The present study is also unique in that measure-

ments were taken in two distinct sessions up to 2 weeks apart.

BP and maximum aortic diameter were the two variables directly measured by the observers and therefore the only variables that were prone to observer bias. The low CV_{ME} value for these variables indicates that this echo-tracking equipment can be reliably used in the follow-up of AAA maximal diameter. There may, however, be some random error in the values calculated for Ep and stiffness because these are derived values and are thus not directly measured. The use of brachial artery pressure rather than central aortic pressure will tend to underestimate Ep and stiffness.¹⁰ However, the error will be systematic, affecting all patients approximately equally. Invasive measurement of aortic pressure is not practicable for routine compliance follow-up. Most previous studies that used Doppler phase-locked loop echo tracking have assumed that brachial BP is consistently related to aortic pressure.^{7,10,11,18}

Table V. Comparison of coefficients of variation of method error of compliance variables between different studies of subjects with AAA and with no AAA

Study	Subjects (n)	Vessel	Systolic BP (%)	Diastolic BP (%)	Maximum diameter (%)	Diameter change (%)	Elasticity (%)	Stiffness (%)
Hansen et al ¹⁰	8F	Normal	2	3	5	16	21	21
Lanne et al ¹⁸	4M	Normal	—	—	—	—	6*	6*
Wilson et al (present study)	13 F&M	AAA	7	5	3	18	21	18

F, Female; M, male.

*SDs are quoted in the text.

The high CV_{ME} values of both Ep and stiffness must be viewed in the context of the wide range of compliance observed in this particular study group (Table I). For example, Ep varied by a factor of 12.75, ranging from 0.74 to 9.44 10^5 N/m², and stiffness varied by a factor of 12.0, ranging from 5.6 to 66.8 10^5 N/m². It should also be noted that, with the exception of BP, the variables measured were all skewed to the right. Because there is no nonparametric equivalent of the CV_{ME} value, the effect of this skewness on the values of CV_{ME} cannot be ascertained. However, if a logarithmic transformation had been applied to the data before the CV_{ME} value was calculated, the resultant CV_{ME} value would have been substantially reduced. For example, the nontransformed CV_{ME} value from observer A for intraobserver stiffness was 32% and for observer B, 25.6%. After transformation, these CV_{ME} values were 10.2% and 8.6%, respectively. The use of the CV_{ME} value calculated from transformed data does not allow direct comparison of variabilities with previous studies. However, it does suggest that the Bland and Altman¹⁷ test for CV_{ME} value is not applicable to skewed data. More importantly for this study, it also suggests that the high level of variation is in fact due to the large variation of Ep and stiffness within the study population rather than because of the technique. The diameter and compliance variations that were observed between visits in study 2 may also reflect a certain degree of real variation in AAA wall movement.

When the raw data were examined, there were two particular subjects in whom markedly different diameters were measured; these patients were difficult to scan because of obesity and cardiac and respiratory disease. We did not remove these subjects from the study because it would have biased the assessment of reproducibility. Nevertheless, approximately 10% of these study subjects could not be satisfactorily scanned because of the factors mentioned earlier. Excluding

such patients would have increased the apparent reproducibility of the technique.

The longitudinal view of the AAA was more informative than the transverse because it allowed a true anteroposterior measurement to be made perpendicular to the aneurysms' long axis. Three compliance measurements were made at each examination. Each was slightly different because of slightly differing BP and because of the cursors inevitably locking onto different layers of the wall. Slight changes in the angle of the probe may also have increased the variability of diameter change, but this was not investigated specifically in this study.

The echo-tracking technique involves placing the cursors onto the echoes of the anterior and posterior walls while the vessel is moving with each cardiac cycle. Tracking of the same points within the wall structure is difficult because the quality of the B-mode imaging does not allow easy differentiation between thrombus, calcification, intima, and media. It is likely that improvements in the image quality and echo-tracking technology will reduce the effect of these factors on reproducibility.

The learning curve associated with echo-tracking compliance measurements was steep for observer A who had no previous experience with ultrasonic scanning. However, intensive training by radiology staff in the recognition of abdominal structures and variations in AAA wall morphologic features meant that the curve leveled off after about 3 months. At this point, the measurements from observer A were within 2 mm of those reported by the ultrasound department. Observer B was subsequently taught the technique by observer A. This may have introduced some systematic bias into the study, although observer B had previous experience scanning AAA, thus reducing the learning curve considerably. At the time of the study, observer A had 2 years of experience with the equipment; observer B had 3 months of experience because it was not possible to

The Relationship Between Abdominal Aortic Aneurysm Distensibility and Serum Markers of Elastin and Collagen Metabolism

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Background: abdominal aortic aneurysm (AAA) distensibility may be an independent predictor of growth and rupture, possibly because it reflects changes in aortic wall structure and composition.

Aim: to determine whether AAA distensibility is related to circulating markers of elastin and collagen metabolism.

Methods: sixty-two male patients of median age (IQR) 68 (65–72) years with asymptomatic AAA of median (IQR) diameter 42 (37–45) mm were prospectively studied. Pressure-strain elastic modulus (E_p) and stiffness (β) were measured using an ultrasonic echo-tracker (Diamove). Serum elastin peptides (SEP), plasma elastin- α_1 -antitrypsin complex (E-AT), procollagen III-N-terminal propeptide (PIIINP) were measured by enzyme-linked immunoassay.

Results: age and smoking adjusted E_p and β were significantly inversely related to SEP ($r = -0.33$ and $r = -0.31$ respectively, both $p < 0.02$) and E-AT ($r = -0.27$ and $r = -0.27$ respectively, both $p < 0.05$) both of which indicate elastolysis. By contrast, there was a significant positive correlation between PIIINP, indicative of increased collagen turnover, and both E_p and β (both $r = 0.45$, $p < 0.01$ unadjusted correlations).

Conclusion: increased elastolysis is associated with increased AAA wall distensibility; whereas increased collagen turnover is associated with reduced distensibility.

Key Words: Aneurysm; Elasticity; Elastolysis; Collagenolysis.

Introduction

Abdominal aortic aneurysm (AAA) distensibility may be an independent predictor of growth and rupture, possibly because it reflects changes in aortic wall structure and composition.^{1,2} There is general agreement that AAA formation is associated with degradation and/or redistribution of elastin and collagen in the media.³ This, in turn, appears to be due to an increase in elastase and collagenase activity.⁴ Elastolysis has been shown previously to be associated with increased levels of serum-elastin-peptides (SEP).^{5–7} Alpha₁-antitrypsin (AT) inhibits circulating elastase by forming elastase-alpha₁-antitrypsin complex (E-AT) and increased serum E-AT levels may also be indicative of increased elastolysis.^{7,8} Increased type III collagenase activity has been linked to AAA growth, and possibly rupture.^{4,9–11} Increased collagen turnover has been associated with an increase in serum type III

procollagen aminoterminal propeptides (PIIINP) and high levels of PIIINP have been found in patients with AAA.^{9–12} The aim of this study was to determine whether AAA distensibility is related to circulating markers of elastin (SEP, AT, E-AT) and collagen (PIIINP) metabolism.

Methods

Arterial distensibility describes the relationship between fractional diameter (D) change and blood pressure (P).^{13–15} Specifically, pressure-strain elastic modulus (E_p)² is defined as:

$$E_p = K \times (P_{\text{systolic}} - P_{\text{diastolic}}) / [(D_{\text{systolic}} - D_{\text{diastolic}}) / D_{\text{diastolic}}]$$

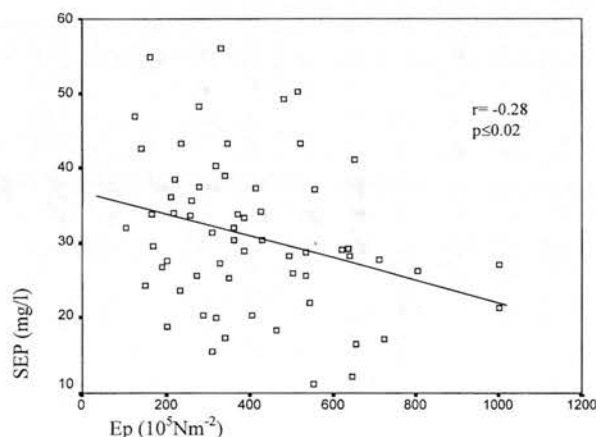
where $K = 133.3$, and stiffness (β)^{16,17} as:

$$\beta = \ln(P_{\text{systolic}} / P_{\text{diastolic}}) / [(D_{\text{systolic}} - D_{\text{diastolic}}) / D_{\text{diastolic}}]$$

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Table 1. Markers of elastin and collagen metabolism.

Variable	Median	IQR
Elastin-peptides (SEP) (mg/l)	29.4	25.0–37.4
Elastase α_1 -antitrypsin (E-AT) (mg/l)	5.7	4.2–7.6
α_1 -antitrypsin (AT) (g/l)	1.3	1.2–1.4
PIIINP-collagen (mg/l)	34.5	25.7–42.1

**Fig 1.** Spearman's rank correlations between Ep and serum elastin peptides.

Both Ep and β are inversely related to distensibility.^{18,19}

The use of the echo-tracking ultrasound system (Diamove, Teltec AB, Sweden) has been described in detail previously.^{14,18,20} A 3.5 MHz linear array transducer was used to provide a real-time B-scan image of a longitudinal section of the AAA at the point of maximal antero-posterior (AP) diameter. The pressure-diameter curve was registered on the computer in real time. Blood pressure was measured in the right brachial artery by sphygmomanometry^{21,22} and pulse pressure, diameter change (Dch), Ep and β were calculated by the software.

Non-commercial enzyme-linked immunosorbent assays (ELISA) were used for determination of SEP, AT and E-AT as previously described.⁶ PIIINP levels were measured by the method of Jensen²³ and Ristelli.²⁴

Age was normally distributed; however, diameter,

Ep and β were not. Therefore, non-parametric descriptors and log transformed analyses of Ep and β were performed (SPSS-9). Results for Spearman's rank correlation on untransformed data and Pearson partial correlation adjusted for age and smoking were very similar. Pearson's correlation cannot easily be illustrated and so scatterplots of Spearman's correlation have been used. Smoking status was defined as current or ex-smokers; there were no non-smokers. A probability level of <0.05 was taken to denote statistical significance. The study received local ethics committee approval and was reported to the Danish Central Control of Registers. All patients provided written, informed consent.

Results

There were sixty-two males of median (IQR) age 68 (65–72) years with screen-detected AAA of median (IQR) antero-posterior (AP) diameter 42 (37–45) mm. The median (IQR) Ep was 3.56 (2.52–5.35) 10^5 Nm^{-2} and the median (IQR) β was 24.4 (18.5–35.8) arbitrary units (a.u). Circulating markers of elastin and collagen metabolism are shown in Table 1.

After adjusting for age and smoking status, Ep and β were significantly inversely related to both SEP and E-AT (Table 2. Figures 1 and 2 represent the unadjusted correlations). By contrast, there was a significant positive correlation between PIIINP and both Ep and β (Table 2, Fig. 3 unadjusted correlations). Dmax was not related to any of the circulating markers.

Discussion

The principal findings of the present study were that after adjusting for age and smoking status, both Ep and β were significantly inversely related to circulating SEP and E-AT; that is, patients with evidence of increased elastolysis had more distensible aneurysms. By contrast, AAA distensibility was inversely related

Table 2. Pearson's partial correlation coefficients (*p* values) for serum markers of matrix degradation, distensibility and diameter, adjusted for age and smoking status.

Serum markers	Elasticity	Stiffness	Diameter
Elastin-peptides (SEP)	–0.33 (0.01)	–0.31 (0.02)	–0.20 NS
Elastase α_1 -antitrypsin (E-AT)	–0.27 (0.04)	–0.37 (0.04)	0.11 NS
α_1 -antitrypsin (AT)	–0.10 NS	–0.06 (NS)	–0.08 NS
PIIINP-collagen	0.45 (0.01)	0.45 (0.01)	0.21 NS
Elasticity	—	—	0.49 (0.01)
Stiffness	—	—	0.46 (0.01)

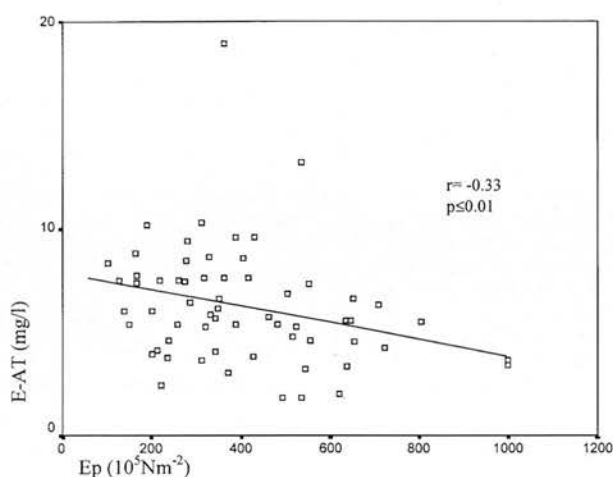


Fig. 2. Spearman's rank correlation coefficients between elastase α_1 -antitrypsin (E-AT) and Ep.

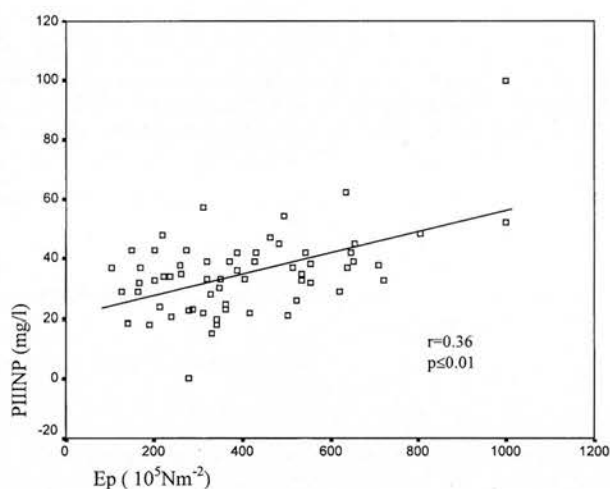


Fig. 3. Spearman's rank correlation coefficients between propeptide of type III procollagen (PIIINP) and Ep.

to PIIINP, a marker of increased collagen neosynthesis.

Previous work from this group has shown that AAA of similar size exhibit markedly different degrees of distensibility.¹ We had hypothesised that this was due to differences in the absolute and relative amounts of elastin present in the aorta. This current study may now provide support for that contention in that AAA distensibility was significantly inversely related to circulating of E-AT complex. This complex may be indicative of smoking-induced lung damage; however, adjustment for smoking did not diminish this relationship. At present it is not possible to determine absolutely whether this elastase originates in aortic or lung tissue. Previous authors have shown markers of elastin degradation to be indicative of aortic matrix degeneration.^{6,25,26} The SEP ELISA measures a wide spectrum of peptides, including some which may be

more specific to the aorta (serine-, cysteine- and metallo-dependent proteases). Our finding that SEP levels were also inversely related to distensibility suggests that distensibility may indeed be reflecting aortic elastin degradation, induced by other proteases than elastin. SEP and E-AT were not related to AAA diameter, suggesting that AAA wall degradation may not be uniform within AAA of the same diameter.

Our preliminary longitudinal data had also suggested that distensible AAA were more likely to rupture. Specifically, while most aneurysms tend to become less distensible as they expand, those that fail to grow stiffer as they enlarge or become suddenly more distensible appear to be at particularly high risk of rupture. This observation can also be explained in terms of the present data on PIIINP.

An increasing level of PIIINP, indicating collagen neosynthesis, was related to increasing Ep and β (reduced distensibility). This new collagen is less distensible than the elastin it is replacing. Previous workers have suggested that high levels of PIIINP are in fact associated with AAA expansion and rupture.⁹ While this appears to contradict our previous contention that AAA undergoing an increase in distensibility are more likely to rupture, it is possible that the strength of the new collagen may be compromised in some of the subjects because of the higher rate of turn-over.⁴ Satta *et al.*⁹ found that in AAA development, PIIINP and diameter increased exponentially with time and, in cases of rupture, rate of collagen turn-over was significantly higher than in non-ruptures. In some cases very high levels of collagen neosynthesis and PIIINP release may, in fact, be associated with failure of collagen maturation, depauperisation of fibres and the laying down of collagen that is structurally weak. Furthermore, those aneurysms which fail to lay down collagen as they grow may be least able to withstand the increased wall tension predicated by the law of Laplace and thus show higher distensibility.

These findings are significant in that they show, for the first time, that distensibility may be indicative of the AAA wall matrix degeneration and regeneration process. The importance of these findings is that distensibility, which is easily measured non-invasively, may provide a more detailed picture of the changing AAA wall matrix than diameter alone. More specifically, distensibility may indicate the terminal breakdown of collagen which eventually leads to rupture of the AAA wall. In conjunction with currently used risk factors, namely diameter, expansion rate and symptoms, this may allow surgeons to further specify which AAA require immediate surgery and which can safely expand or remain at a size previously thought

dangerous, with little risk of rupture. It is quite possible, however, that each AAA is unique and it is the change in distensibility within each aneurysm that is of greater significance than differences between a level of "normal" distensibility and that of the aneurysm.

A large prospective observation study is ongoing, investigating distensibility, diameter, expansion and outcome. This study will provide much more detail of the predictive value of distensibility in relation to risk of rupture, need for operation and safe expansion without rupture. In addition, a larger study investigating changes in markers of elastolysis and collagenolysis in relation to the natural history of AAA diameter and distensibility is required.

Acknowledgements

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Comparison of Brachial Artery Pressure and Derived Central Pressure in the Measurement of Abdominal Aortic Aneurysm Distensibility

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Objective: AAA distensibility (E_p , β) may predict growth and risk of rupture. However, distensibility measurements based on brachial rather than central pressure may be inaccurate. Our aim was to compare AAA distensibility using non-invasive brachial and derived central aortic pressure.

Design: brachial and central pressures were measured prospectively by automated sphygmomanometry (Omron) and pulse wave analysis (SphygmoCor) respectively. AAA distensibility was calculated using brachial (E_p^b , β^b) and central (E_p^c , β^c) pressures by ultrasonic echo-tracking (Diamove). Twenty-eight patients (18 males) were selected on a first come basis from a larger study of AAA patients. There were no exclusion criteria, so 54% had cardiac dysfunction (MI, angina) and 14% were hypertensive (BP>140/90 mmHg).

Results: median (IQR) age was 74 (70–77) years, median AAA (IQR) diameter was 44 (40–51) mm. Central and brachial systolic pressures were significantly different, [140 (121–153) vs 144 (130–164) mmHg respectively, $p \leq 0.01$]. Central and brachial diastolic pressures were not significantly different [76 (72–86) vs 76 (71–86) mmHg respectively, $p = 0.5$]. E_p^c (3.0, [2.2–4.9]) and β^c (22.2 [15.5–33.2]) were significantly lower than E_p^b (3.6, [2.4–5.1] 10^5Nm^{-2}) and β^b (24.7 [17.1–33.0] a.u., all $p < 0.001$). Brachial and central derived distensibility remained significantly different after adjusting for age and diameter ($p < 0.001$).

Conclusion: the use of brachial pressure leads to a small, systematic overestimate of E_p (18%) and β (11%) independent of age and AAA diameter. This systematic error will not bias follow-up of changes in distensibility.

Key Words: Abdominal aortic aneurysm; Blood pressure; Distensibility.

Introduction

The decision to operate on a patient with an asymptomatic abdominal aortic aneurysm (AAA) involves weighing the risks of rupture against those of operative repair. Although cohort studies indicate that rupture is related to maximum AAA diameter (D_{\max}), growth rate and blood pressure (BP), none of these variables reliably predict the behaviour of individual aneurysms.¹ As no AAA is entirely free from risk of rupture, a variable that provides a more precise quantification of risk is required.

Previous work has suggested that, in addition to maximal diameter, AAA wall distensibility, expressed as pressure-strain elastic modulus (E_p) and stiffness

(β), measured by means of a commercially available ultrasound echo-tracking system (Diamove), may be related to future growth rate and risk of rupture.² We² have previously shown that when AAA diameter and aortic stiffness increase concomitantly (decreasing distensibility), aneurysm rupture is less likely than when AAA diameter increases but stiffness decreases (increasing distensibility). We³ also reported that AAA wall distensibility might indicate matrix degeneration in terms of collagen and elastin integrity, since distensibility decreases with elastin degeneration and collagen deposition, but in the final stages of collagen breakdown distensibility increases.³ These findings suggest that serial simultaneous measurement of diameter and distensibility might provide a better understanding of the degeneration occurring in the aortic wall matrix than simply assessing diameter. They also suggest that the absolute value of AAA distensibility is less important than its change over time.

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Arterial wall compliance describes the change in volume of a segment of artery, in relation to pulsatile change in BP.⁴ However, measurement of change in wall thickness in response to change in pressure and vessel volume is necessary to calculate true vessel compliance.⁴ At present, neither variable can be reliably measured in the aorta *in vivo*. Arterial wall distensibility, which describes the relationship between relative diameter change and pressure, has been used by a number of workers⁵⁻⁷ as a "surrogate" measure of compliance.

Ep^4 is a measure of the structural distensibility of the artery, rather than a measure of the elasticity of the arterial wall material,⁷ where:

$$Ep = K (P_{\text{systolic}} - P_{\text{diastolic}}) / [(D_{\text{systolic}} - D_{\text{diastolic}}) / D_{\text{diastolic}}]$$

and $K = 133.3$, P = pressure and D = aortic diameter.

Stiffness index (β)⁸ also describes the visco-elastic behaviour of arteries within the physiological pressure range, where:

$$\beta = \ln(P_{\text{systolic}} / P_{\text{diastolic}}) / [(D_{\text{systolic}} - D_{\text{diastolic}}) / D_{\text{diastolic}}]$$

β is less pressure dependent than Ep ,⁸ both are inversely related to distensibility and compliance. These concepts are discussed more fully in two reviews.^{9,10} Both can be measured using ultrasonic echo-tracking equipment described in the Methods section.

Poiseuille's law describes the flow of fluids and shows that blood "flow is directly proportional to the difference between inflow (aortic) and outflow (peripheral) pressures".¹¹ Further studies have shown that systolic pressure increases along the arterial tree from the aorta to the peripheral arteries by 10–35 mmHg¹²⁻¹⁴ due to differences in vessel stiffness and wave reflections. In contrast diastolic pressure and median arterial pressure (MAP) fall only slightly – which provides the pressure gradient for forward flow of blood along a pressure gradient.¹²⁻¹⁴ The net result is an increase in pulse pressure peripherally.¹²⁻¹⁴

The aim of this study, therefore, was to compare AAA distensibility (Ep and β) calculated using brachial BP with that calculated from derived central BP (estimated by pulse wave analysis) using two non-invasive methods of BP measurement, as would be the case in a clinical setting. Thus any possible underestimation of BP due to sphygmomanometry technique would be constant between the techniques.

Methods

Central blood pressure can now be assessed non-invasively using pulse wave analysis (PWA). PWA allows accurate recording of peripheral arterial pressure waveforms, and construction of the corresponding central pressure waveform and augmentation index. The technique uses applanation tonometry, which is based on the principle that when opposing curved surfaces of a vessel are flattened until parallel with each other, circumferential pressures are equalised. In other words, when an arterial wall is flattened (applanated) by the tip of the tonometer, the contact pressure between the transducer and the wall equals the intra-arterial pressure. This technique can be accurately applied to peripheral arteries such as the radial or the carotid, and can also be used on the femoral artery to derive aortic pulse wave velocity. The peripheral waveform is recorded and transformed into the corresponding central waveform using an integral transfer function, which has previously been validated using invasive recordings.¹⁵⁻¹⁷ Both waveforms can then be analysed and a number of variables measured including central systolic, diastolic, mean arterial and pulse pressures.

Twenty-eight subjects (18 male) were studied. These subjects had known AAA and were recruited on a "first-come" basis from a larger prospective study investigating AAA distensibility and rupture. In order to truly replicate the normal clinical setting there were no exclusion criteria and, as a result, 54% of these patients had some cardiac dysfunction (angina or MI). Only 14% had hypertension according to the British Hypertension Society guidelines (pressure >140/90 mmHg).¹⁸

PWA was used to determine central pressure non-invasively (Sphygmocor, SCOR; PWV Medical, Sydney, Australia).¹⁹ Pressure waveforms were recorded from the radial artery using a high fidelity micro-manometer (SPC-301, Millar Instruments, Texas, U.S.A.) and fed directly into a portable micro-computer.²⁰ The integral system software allowed on-line recording of the radial waveform and, after 20 sequential waveforms were collected, an averaged peripheral and corresponding central waveform was generated. Central aortic pressure was then calculated from the waveform²¹ using a validated transfer function.^{15-17,20} To evaluate the quality of the recorded wave, the software calculates two parameters of the wave variability allowing the observer to accept the waveform according to pre-stated levels of acceptable variability; namely wave amplitude >100 mV, standard deviation of systolic and diastolic peak <5%. The validation and reproducibility of the SphygmoCor tech-

nique in pulse wave analysis and the measurement of central pressure has been discussed previously and found to be acceptable.^{20,22} There was a short time delay between tonometric and brachial pressure measurements; however, both were carried out alternately first or second to avoid a time-dependent bias.

BP was measured from the brachial artery in the right arm using an oscillometric sphygmomanometer (model 711, Omron, Japan); and phase locked loop echo-tracking (Diamove, Teltec, Sweden) was used to measure aortic E_p and β . The echo-tracking ultrasound system has been described in detail previously.^{9,10} Briefly, a 3.5 MHz linear array transducer was used to provide a standard real time longitudinal B-scan image of the AAA at the point of maximal antero-posterior (AP) diameter. The vessel walls were tracked after initial placement of a cursor within the vessel. A phase-locked loop restored the position of an electronic gate relative to the moving echo while the compensatory movement of the gate yielded the movement of the echo.

Data acquisition and analysis were carried out on a Pentium computer (DCS, Edinburgh). The pressure-diameter curve was registered on the computer in real time and at least three consecutive waves were analysed. The Diamove software automatically identified the start and end of each cardiac cycle. The operator manually selected the waveforms of interest and an average wave was produced. Brachial artery pressures were entered and the calculated variables, including E_p and β , were then displayed on the screen. Distensibility calculated using derived central pressure is referred to as E_p^c and β^c , whereas distensibility calculated using brachial pressure is referred to as E_p^b and β^b .

Statistical analysis was carried out using SPSS Base 8.0.²³ The data were skewed so median and interquartile ranges (IQR) were calculated. Spearman's rank correlation was used to examine the correlation between brachial and central variables, Wilcoxon signed rank test was used to evaluate the differences between central and peripheral derived variables. In order to examine whether age and diameter confounded the observed relationships, the data were first logarithmically transformed to normality. Linear regression was then used to calculate predicted (log) distensibility adjusted for the effect of age and diameter.

Results

The mean (range) age of the subjects was 74 (63–84) years and the median (interquartile range (IQR)) AP

diameter was 44 (40–51) mm. The median (IQR) brachial pressures were systolic 144 (130–164) mmHg, diastolic 76 (71–86) mmHg, and the median (IQR) central pressures were systolic 140 (121–153) mmHg, diastolic 76 (72–86) mmHg. The amplification ratio (peripheral PP:central PP) was 1.1.

There was a significant positive correlation between the central and brachial pressures (Table 1). Derived central systolic pressure, pulse pressure and MAP were significantly higher than the brachial equivalents (Table 1). There were no differences with regard to diastolic pressure ($p=0.5$).

There was a significant correlation between E_p^c and brachial E_p^b ($r=0.90$, $p\leq 0.001$) (Fig. 1) and between β^c and β^b ($r=0.90$, $p\leq 0.001$) (Fig. 2). However, the Wilcoxon signed rank test showed that median E_p and β were significantly higher ($p\leq 0.01$) when using brachial pressure rather than central pressure: [E_p^b 3.6 (2.4–5.1) vs E_p^c 3.0 (2.2–4.9) 10^5Nm^{-2} , $p\leq 0.001$]; [β^b 24.7 (17.1–33.0) vs β^c 22.2 (15.5–33.2) a.u., $p\leq 0.01$].

In order to examine whether the difference in distensibility derived from central and brachial pressures were confounded by age or AAA diameter, predicted log values for central and brachial-derived distensibility adjusted for age and diameter were calculated and compared. The differences between distensibility calculated using brachial and derived central pressures remained significant (both $p\leq 0.001$). Median (IQR) E_p^b predicted from brachial pressure was 1.22 (1.08–1.45) 10^5Nm^{-2} , and E_p^c predicted from central pressure was 1.11 (0.94–1.35) 10^5Nm^{-2} . Similarly, β^b predicted from brachial pressure was 3.18 (3.05–3.37), and β^c predicted from central pressure was 3.07 (2.94–3.32).

Discussion

This study compares, for the first time, the use of non-invasive brachial artery pressure and derived central aortic pressure in the measurement of AAA distensibility.

Previous work using invasive intra-aortic pressure measurement and non-invasive assessment of aortic distensibility (ultrasonic echo-tracking) suggested that using peripheral blood pressure to calculate distensibility underestimates E_p and β by 25–30%.^{24,25} However, in one of these studies²⁴ systolic pressure was the same or lower in the brachial artery than in the aorta, diastolic pressure higher in the brachial artery, and consequently pulse pressure was lower in the brachial artery. In the second study,²⁵ systolic and diastolic pressures were higher in the brachial artery

Table 1. Wilcoxon signed rank test comparing brachial and central pressures and pressure-strain elastic modulus (Ep) and stiffness (β) derived from brachial and central pressures.

	Brachial Median (IQR)	Central Median (IQR)	% Differences	Significance (Two tailed)
Systolic (mmHg)	144 (130–164)	140 (121–153)	+ 3	0.001
Diastolic (mmHg)	76 (71–86)	76 (72–85)	0	0.5
Pulse pressure (mmHg)	65 (50–79)	60 (44–75)	+ 8	0.001
Mean arterial pressure (mmHg)	100 (89–110)	99 (89–106)	+ 1	0.003
Ep (10^5Nm^{-2})	3.6 (2.4–5.1)	3.0 (2.2–4.9)	+18	0.001
β (a.u.)	24.7 (17.4–33.0)	22.2 (15.5–33.2)	+11	0.010

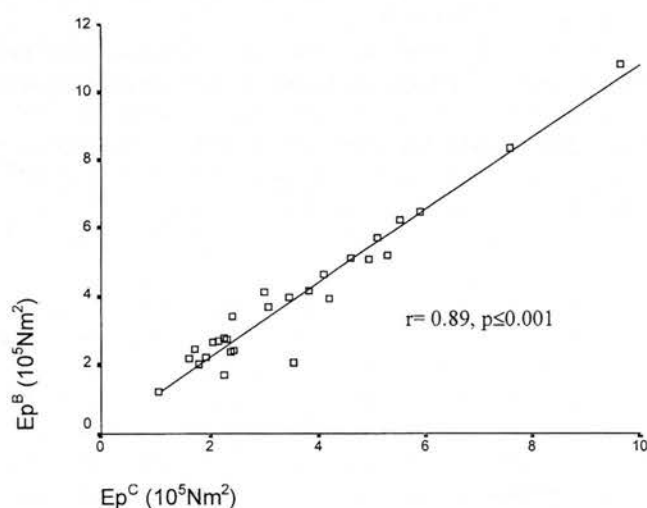


Fig. 1. Scatter plot of correlation between Ep calculated using brachial and central aortic pressures (r =Spearman's rank correlation).

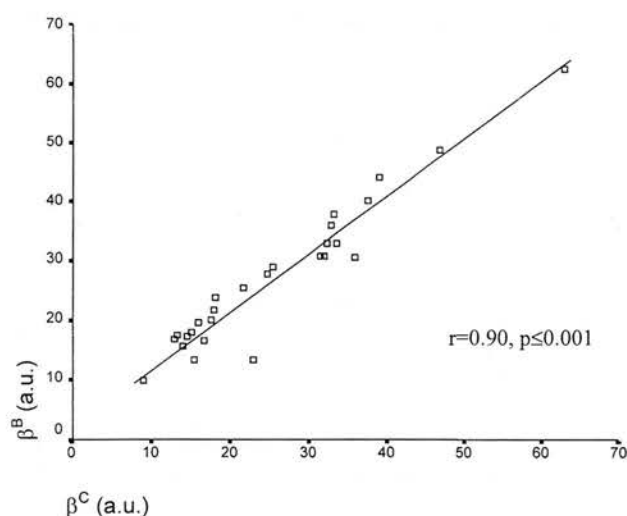


Fig. 2. Scatter plot of Spearman's rank correlation between β calculated using brachial and central aortic pressures.

than in the aorta, and pulse pressure was lower in the brachial artery. Not only are these findings difficult to explain physiologically, but they are also in contrast

to the majority of other data.^{11–14} The most likely explanation may be that because the authors compared invasive aortic pressure measurement with sphygmomanometrically determined brachial artery pressure, the error was dependant on the method of measurement rather than the site of measurement. Indeed, the inaccuracy of sphygmomanometric blood pressure measurements has been previously reported.²⁶

As the pressure wave travels through the arterial tree from the large, elastic arteries to the smaller, muscular vessels, the speed and amplitude of the wave increase because of decreasing vessel compliance. The pressure contour also becomes distorted along the arterial tree: the systolic portion becomes narrowed and elevated; the incisura is damped and eventually disappears: a hump appears in its place in the diastolic portion. This damping of the high frequency components of the pressure wave is attributed to the viscoelastic properties of the arterial wall. Reflection, vascular tapering and transmission velocity enhance the peaking of the pressure wave. The result is that in the young there is a pronounced difference in central and peripheral pressures, systolic pressure increasing distally whilst diastolic pressure remains essentially unchanged,²⁷ i.e. there is amplification of the waveform (Fig. 3).

Ageing of the arterial tree reduces vessel distensibility (increases stiffness) and markedly reduces the difference between central and peripheral systolic pressure while increasing pulse pressure, especially in the aorta. This is because stiffer arteries transmit the pressure wave at a higher velocity, i.e. pulse wave velocity is increased. The result is that a larger than normal reflected pressure wave returns to the heart earlier, augmenting late systolic peak pressure.¹² Thus, whilst age increases aortic systolic pressure, peripheral systolic pressure is much less affected, so the gradient between central and peripheral systolic pressure is reduced.¹⁴ Pauca *et al.*¹⁴ examined a group of subjects aged 48–77 (median 61) years and found the ascending aortic systolic pressure to be 12 mmHg lower than

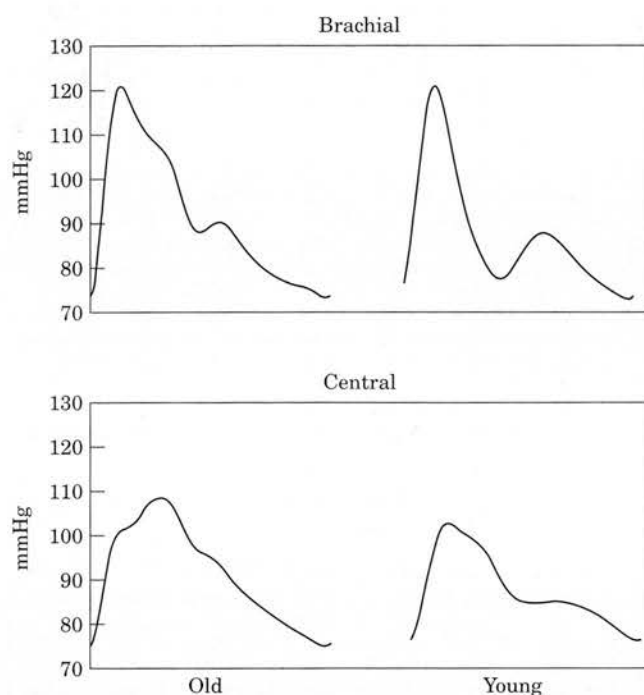


Fig. 3. Central arterial waveform (lower panel) and peripheral waveform (upper panel) in a young (right) and an elderly (left) subject. Reproduced from Wilkinson *et al.* 1998.¹⁷

radial systolic pressure and ascending aortic diastolic pressure to be 1 mmHg higher than radial pressure. In the present study, the median central-brachial pressure difference was 6 mmHg for systolic pressure but there was no difference in diastolic pressure. The amplification ratio (peripheral pulse pressure:central pulse pressure) of 1.1 reflects the older age of our study population (68–84, median 74 years).

Aortic pressure was that in the aortic arch and not at the site of the AAA. Abdominal aortic pressure remains extremely difficult to measure non-invasively at present. However, the PWA-derived ascending aortic pressure is the closest approximation available and is considerably closer than the brachial artery. Previous work has suggested that in evaluating ascending aortic dilation and distensibility in Marfan's syndrome, the pulse pressure in the carotid artery may be more useful than that from the brachial artery.²⁸ It may also be the case that aortic arch pressure is more representative of pressure at the site of the AAA than that at the brachial artery. However, this requires further study and a comparison of distensibility calculated using invasive aortic pressure at the site of the AAA with that using derived central pressures.

The principle finding of the study was that use of brachial pressure as opposed to central aortic pressure significantly increased E_p by 18% and β by 11%. This is of a similar magnitude to that of the previous

authors.^{10,15} The error was a systematic overestimate of E_p and β ; however, the margin of error in calculation of β was relatively smaller because it is less pressure dependent than E_p . The importance of these findings is that this non-invasive method of aortic wall distensibility measurement can be used successfully in the clinical setting. Use of non-invasive, derived aortic pressure would enhance the accuracy of distensibility measurement; however, the error caused by using non-invasive brachial pressure is deemed small and systematic. Previous findings of this group^{2,3} suggest that routine follow-up of distensibility and diameter could provide a greater understanding of AAA wall degeneration than diameter alone. If this is the case then the systematic nature of the error should not bias the measurements because it is the change in the measurements over time that provides the important information and not the absolute values.

In conclusion, we view the overestimate of E_p and β (by 18% and 11% respectively) to be small and, therefore, acceptable clinically. The linearity of the relationship between central and peripherally derived distensibility shows that the error is a small and systematic overestimate and would not bias follow-up comparison of changes in distensibility within each patient. However, since the discrepancy between central and peripheral systolic pressure (i.e. pressure amplification) is age-dependent, greater differences between E_p^b/β^b and E_p^c/β^c may occur in younger individuals, and care must be exercised when comparing measures of distensibility based on peripheral blood pressure measurements between age groups.

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